TECHNICAL SUPPORT DOCUMENT

REPORT TO THE AIR RESOURCES BOARD ON CADMIUM

PART C - PUBLIC COMMENTS AND RESPONSES

December 1986

Southern California Edison Company

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January 21, 1986

Mr. William V. Loscutoff, Chief
Toxic Pollutants Branch
Air Resources Board
Attention: Cadmium
P. O. Box 2815
Sacramento, California 95812

Dear Mr. Loscutoff:

SUBJECT: Draft Report to the Scientific Review Panel on Cadmium

Southern California Edison Company has reviewed the draft document entitled "Report to the Scientific Review Panel on Cadmium" and would like to submit these brief comments on several important issues which are addressed in this report. The issues of primary concern are the cadmium emission estimates from oil-fired power plants and the methods used to estimate the carcinogenic risks from cadmium.

In addition we would like to submit for your information the transcripts from the recent U.S. Environmental Protection Agency's public hearing on the EPA Notice of Intent to List Cadmium Under Section 112 of the Clean Air Act.

Edison regrets that we were unable to meet the stringent deadline for comment submittal. We believe, however, that the time provided for public review, which has been on the order of two weeks, is not sufficient to allow the level of review and comment these important documents require.

THE ABOVE MENTIONED ATTACHMENT OF TRANSCRIPTS OF EPA HEARING ON NOTICE OF INTENT TO LIST CADMIUM UNDER SECTION 112 OF THE CLEAN AIR ACT CAN BE FOUND AS APPENDIX F OF COMMENTS FROM THE CADMIUM COUNCIL.

EMISSION ESTIMATES

ARB has estimated cadmium emission factors (lb of Cd per lb of fuel burned) from oil-fired power plants by taking an average of estimates from two studies, Taback et al. (1979) and Krishnan and Hellwig (1982). The estimated emission factor was then applied to the residual fuel oil consumption by utilities in 1983 to obtain the emission estimate.

Taback et al. analyzed flue gas particulate samples from oil fired power plants in the South Coast Air Basin. Estimates of cadmium emissions were made for four of the tests. Since total fuel oil consumption was recorded during these tests, it is possible to calculate fuel oil concentration of cadmium. This data is presented in Table 1.

TABLE 1. Cadmium Emission Estimates Based on Stack Sampling. (Taback et al. 1979)

TEST#	Emission Rate (lb/hr)	Fuel Oil Consumption Rate (lb/hr)	Calculated Fuel Oil Concentration
11	0.01	218,765	0.0457 ppm
12	< 0.1	220,497	< 0.453 ppm
32	< 0.1	210,857	< 0.474 ppm
33	0.08	209,055	0.383 ppm

Krishnan and Hellwig (1982) have estimated emissions from residual oil-fired boilers equipped with various types of control devices. Emission estimates are given in terms of picograms per joule of energy content in the fuel. ARB has assumed an energy content of fuel oil of 152,000 Btu/gallon which is equivalent to 1.6×10^8 joules/gallon. It is possible to calculate the concentration of cadmium in fuel oil which would produce the estimated emissions. This is shown in Table 2.

TABLE 2. Cadmium Emission Estimates from Krishnan and Hellwig (1982).

Boiler Type/ Control Device	Emission Rate (pg/J)	Equivalent* Concentration In Oil
Utility/ No Controls	71.8	3.20 ppm
Utility/ Electrostatic Precipitator	14.4	0.642 ppm

* Cadmium concentration in fuel oil which would give equivalent stack emissions (assumes no control device).

ARB has estimated an average emission factor of approximately 3.67×10^{-6} lb/gal or 0.46 ppm in fuel oil. This was apparently obtained by averaging (1) the highest identified emission rate from the Taback study (and excluding the other measured value which was about 10 times lower) and; (2) the estimate from the Krishnan study which applies to utility boilers with ESP control (even though utility boilers in California are not equipped with these devices).

Edison has measured cadmium concentrations in fuel oil at two power plants and has found an average concentration of approximately 0.1 ppm. There is a great range in trace element concentrations in crude and fuel oils and "typical" concentration estimates may be significantly different from measured values at a specific plant. If the two measured values obtained by Taback et al. are averaged (the "less than" values are excluded) a fuel concentration of 0.21 ppm is obtained and this agrees fairly well with the Edison data.

The emissions estimates presented by Krishnan and Hellwig should be viewed very cautiously. Although several studies of trace element emissions are cited by the authors, there is no specific reference for the data or methods used to calculate emissions of cadmium and other trace elements from oil-fired power plants. Thus the emissions factors are essentially unreferenced. The authors also point out that the emission factors are "only general estimators of the actual emissions and could vary widely from plant to plant".

In view of the shortcomings of the Krishnan and Hellwig emissions factors and the fact that they are not in agreement with measured power plant emissions and fuel oil concentrations obtained at California plants, it would be preferable to use the data from Taback et al. in estimating cadmium emissions from residual oil-fired power plants. It must be recognized that emissions at any specific facility could be lower and that the emission factor is only an estimate.

The ARB's emissions estimates for residual fuel oil-fired power plants should be recalculated using the data from Taback et al. and excluding the emissions factors from Krishnan and Hellwig which are not in good agreement with data from California power plants.

EVALUATION OF THE CARCINOGENIC RISKS OF CADMIUM

In June of 1985, the U.S. Environmental Protection Agency released a final report addressing the mutagenicity and carcinogenicity assessment of cadmium. In this report EPA states:

> "Altogether, the epidemiologic data appear to provide limited evidence of lung cancer risk from exposure to cadmium, based on the IARC classification system...and the U.S. Environmental Protection Agency's Proposed Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1984)".

IARC has described "limited evidence" as "evidence of carcinogenicity, which indicates that a causal interpretation is credible, but that alternative explanations, such as chance, bias, or confounding, could not adequately be excluded". EPA derived a unit risk estimate for cadmium of 1.8×10^{-3} using the data from a study by Thun et al. (1985).

DHS, after evaluating the same study by Thun et al., has concluded that "there is sufficient evidence for carcinogenicity in humans." DHS has also concluded that the range of unit risk estimates for cadmium is from 2.3×10^{-3} to 21×10^{-3}. The upper limit of this range is more than 10 times higher than the unit risk recommended by EPA.

Questions therefore arise with respect to: (1) Why does the DHS interpretation of the data differ both qualitatively and quantitatively from the interpretation of EPA?, and (2) How strong is the evidence that cadmium is a human carcinogen?

Risk estimates developed by both EPA and DHS are shown in Table 3.

TABLE 3. Comparison of Unit Risk Estimates for Cadmium Derived by DHS and EPA.

SOURCE	UPPER LIMIT	BEST ESTIMATE	LOW ESTIMATE
EPA	3.5×10^{-3}	1.8×10^{-3}	not calculated
DHS (uncorrected)	18×10^{-3}	2.0×10^{-3}	1.6×10^{-5}
DHS (corrected for CdO)	21×10^{-3}	2.3×10^{-3}	1.8×10^{-5}

It should be noted that although EPA calculated a 95% upper confidence limit (UCL) for cadmium potency, this was not suggested as the best estimate of potency. EPA felt that the 95% UCL was "an unnecessary added level of conservatism, since the model used already inflates the risk estimate if nonlinear components exist or confounding factors are present". [EPA 1985]

One minor reason for the differences between the EPA and DHS risk estimates is that DHS has corrected exposures on the assumption that the cadmium levels in the Thun et al. paper were reported as cadmium oxide. In fact, the values reported by Thun were reported as cadmium (not the oxide) and this adjustment was incorrect. The last line of Table 1 should therefore be disregarded and these values deleted from the draft report.

The best estimates derived by EPA and DHS are quite similar (2.0×10^{-3} versus 1.8×10^{-3}) in spite of the fact that they are using different models and that DHS has censored the data from the study by excluding any data which does not show an increased cancer risk from cadmium exposure, as discussed below.

The significant differences between the DHS and EPA estimates result from the methods used to calculate upper limits of risk. EPA has used a statistical approach to derive a probabilistic estimate of the upper limit of risk. DHS has used a technique which they refer to as "maximizing the slope" which is not really a model but merely a sensitivity analysis using "worst case" assumptions to derive a non-statistical "worst case" estimate of risk. DHS has derived an upper limit by assuming; (1) that the entire moderate exposure group was exposed to the lowest level of the concentration interval for that group; and (2) that the true cancer response observed in that group may have been higher (i.e. the 95% UCL for the relative risk). DHS also uses a higher estimate of the background rate for lung cancer than is used by EPA in their assessment.

The combined effect of these assumptions is to create a "worst case" estimate of risk which probably has no bearing on the true risk.

The major problem with the model used by DHS is that it cannot accommodate data which indicate no increase in cancer among the exposed population. The low exposure group in the Thun et al. study is a case in point. This data was excluded from the analysis because it did not fit into the model used by DHS and because DHS staff did not "believe" that cadmium exposure could have a health protective effect. In calculating the minimized estimate of the slope for the moderate exposure group, another data point was deleted for the same reasons. This type of data censoring is clearly unscientific. No reasonable justification has been given for this selective use of data. The data for the low exposure group is just as valid as the other data presented in the study. If the model chosen by DHS does not allow for the use of all the data available in the study, then a different model should be chosen. This would be preferable to exclusion of data based on a priori assumptions concerning the shape of the dose response curve. Other models, such as the one used by EPA, do not present this type of problem. Models which allow for the use of all the data should be used by DHS.

The issue of thresholds has not been dealt with adequately in the DHS report. The lack of response of the low exposure group in the Thun study should have stimulated some discussion with regard to the possibility of a threshold phenomenon. This is particularly true in light of the fact that the evidence for mutagenicity of cadmium is very limited. EPA's analysis has shown that a threshold model fits the data as well as a linear dose response model. The possibility of a threshold phenomenon should be evaluated with respect to the Thun data.

Thun has taken steps to estimate the potential effects of smoking and arsenic exposure on the worker population. However, the potential confounding effects of arsenic exposures in the workplace and the combined effects of smoking and arsenic cannot be ruled out as a potential cause of the increased cancer incidence at this time. It must be noted that the actual increase in cancer in the exposed group is fairly small. There were 7 cancers observed versus 4.6 cancers expected in the moderate exposure group. If it were found that these 7 workers with cancer had significantly higher arsenic exposure than the other members of this exposure category, the significance of this this study would have to be reevaluated. This type of nested case/control study is currently being performed by Dr. Thun. DHS should await the results of this study before finalizing their health effects evaluation.

Given the possible effects of arsenic exposure on the workers in the Thun study and the lack of a consistent dose response relationship in the epidemiological studies, EPA's conclusion of "limited evidence" of lung cancer risk from cadmium appears warranted. This lack of strong epidemiologic evidence, the possibility of nonlinear components in the dose response function, and potential confounding variables played a role in EPA's decision to recommend the maximum likelihood estimate of risk as the best single estimate. DHS should also refrain from recommending upper bound estimates of risk for purposes of extrapolation until the uncertainties in the occupational epidemiology studies can be resolved.

With respect to new data on cadmium and cancer, DHS should also consider obtaining the papers which will be presented at the Fifth International Cadmium Conference in San Francisco on February 4-6, 1986. Presentations by Dr. Thun and Dr. Lamm on February 6 may be of particular interest to DHS staff. Certainly the staff would want to incorporate any new information presented at this meeting before sending the report to the Scientific Review Panel for their review.

Edison appreciates being provided the opportunity to comment on this and other Toxic Air Contaminant documents. Again we apoligize for any inconvenience the minor delay in our submittal may have caused.

Sincerely,

Edward J. Casey

Cadmium Council, Inc.
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212 578-4750

January 29, 1986

Mr. Richard Bode
California Air Resources Board
1800 15th Street
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Sacramento, CA 95812

Dear Mr. Bode:

Enclosed are the Cadmium Council's comments on the Draft Report on Cadmium to the Scientific Review Panel.

Thank you for the opportunity of letting us comment on this document. If you have any questions, please contact me.

Sincerely,

Giovina L. Leone
Director, Environmental Health

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enclosure

BEFORE THE CALIFORNIA AIR RESOURCES BOARD

SACRAMENTO, CALIFORNIA

In the matter of: Draft Report to the Scientific Review Panel on Cadmium

COMMENTS OF THE CADMIUM COUNCIL, INC.

The Cadmium Council, Inc., is a non-profit trade association which represents producers, processors, and industrial users of cadmium in Canada and the United States. The Council's objective with regard to cadmium and health is to develop and disseminate information on the health effects of cadmium in order to assure the safe use of cadmium in the occupational and general environment. This is accomplished through the sponsorship of research on the potential health effects of cadmium exposure, publication of educational and training materials and dissemination of information including current developments in cadmium health research. This data base is subsequently used in the development of occupational and environmental regulations which assure the protection of health while being technologically and economically feasible.

Before continuing, I would like to thank the Air Resources Board on behalf of the members of the Cadmium Council for the opportunity to comment on the draft report on cadmium.

According to the draft, the Air Resources Board recommends that cadmium be listed as a toxic air contaminant because cadmium, stated unequivocally, is a human carcinogen. It is the purpose of these comments to provide the ARB with

information which will cast serious doubt on this statement. So much doubt that the EPA's final Updated Mutagenicity and Carcinogenicity Assessment Document could not provide solid evidence to support an unequivocal conclusion about cadmium's potential as a human carcinogen.

The EPA concluded that there was limited human evidence that cadmium causes lung cancer. The Council feels that even this conclusion is inaccurate in light of new evidence that would be contradictory. In addition, reanalysis of the key epidemiological study is still continuing. And, further work is also being done on confirmation of the key animal study. Until these studies are completed and conclusions are reached, the Cadmium Council feels that there is insufficient evidence that cadmium is a human lung carcinogen. Therefore, we feel that there is presently no scientifically sound basis for listing cadmium as a toxic air contaminant by the ARB.

The ARB's conclusion is a quantum leap from the EPA conclusion even though ARB has found no new studies to support such a definitive claim. In order to better understand why EPA reached a less definitive conclusion, it is important to have some background on the evolution of the EPA assessment document and its purpose.

The first draft of the health assessment document issued in 1983 reviewed the animal and epidemiological evidence concerning the carcinogenicity of cadmium and concluded that cadmium and certain compounds "probably" caused cancer of the prostate in humans. This was a radical departure from the 1981 version which concluded that there was no evidence sufficient to establish that cadmium might be a human carcinogen.

The EPA Cancer Assessment Group withdrew the 1983 draft because of comments which it received indicating significant negative evidence had not been considered which contradicted their conclusion that cadmium probably causes prostatic cancer.

Then in 1984, a second draft health assessment document was issued. After reconsidering their first conclusion, they decided that cadmium could only weakly be associated with prostatic cancer. But, they further concluded that new epidemiological evidence suggested that cadmium may cause lung cancer instead. This conclusion was based primarily on one chronic animal inhalation study by Takenaka and coworkers, but more importantly, on an epidemiological study by Dr. Thun of the National Institute of Occupational Safety and Health. Thun found an excess of lung cancer among workers employed for six months or longer at a U.S. cadmium production facility. The Cadmium Council's comments on this draft are provided as Appendix A.

The EPA Science Advisory Board's Metals Subcommittee met in October of 1984 at the University of Rochester to review the draft document. Among those giving public presentations were experts invited by the Cadmium Council. These experts included Dr. George Kazantzis of the U.K., Dr. Edja Hassler of Sweden, Dr. Steven Lamm from Washington, D.C., and Dr. Lowell White of ASARCO. Upon completion of the presentations, the Metals Subcommittee drafted recommendations for change to the documment (Appendix B). These recommendations were sent to the SAB Environmental Health Committee at which time they were considered along with written comments made by the public. The Cadmium Council submitted additional comments which summarized the presentations made before the Metals Subcommittee (Appendix C).

Even though the letter which was sent to the Administrator of EPA by the SAB agreed with the qualitative findings in the updated document, the SAB qualified their statement with several recommendations for further study.

The SAB was very critical of the quantitative risk assessment which was done by the Cancer Assessment Group recommending several changes and a reanalysis of the data.

Although the SAB found the Takenaka study to be sufficient evidence of cadmium's ability to cause cancer in animals, they felt more information was needed on the actual particle size distribution of ambient cadmium to which the general public would be exposed. This informtion would allow a comparison of the effective dose given to rats in the Takenaka study with typical human exposure for the purpose of quantitative risk assessment.

Of significance is the fact that the SAB recognized the effect of solubility on the bioavailability of various cadmium compounds and thus, a difference in their toxic potency. According to the ARB draft document, recent studies suggest absorption may not be dependant on solubility. The Oberdoerster et.al. (1979) study comparing the lung clearance of cadmium chloride versus cadmium oxide in rats was cited in support of this statement. However, the SAB subcommittee found that lesser solubility does effect the toxicity of some cadmium salts. For example, a rat inhalation study done by Rusch et.al. (1984, Fundam. Appl. Toxicol.) found cadmium red and yellow pigments to be much less bioavailable resulting in decreased absorption and toxicity when compared to cadmium carbonate and cadmium fume.

In addition, the SAB found Dr. Thun's analysis of the confounding effects of smoking to be reasonable and, therefore, not significant. However, Dr. Thun's analysis of arsenic as a confounding variable was criticized for not

using individual arsenic exposure levels. It was further recommended that the joint effect of cigarette smoking and arsenic exposure be examined.

The final document published in June of 1985, had no new evidence to support its conclusion that cadmium may cause lung cancer in humans. And, although the document did not reflect the public comments which criticized the animal and epidemiological studies upon which this conclusion is based, it did change its conclusion that there was sufficient evidence to regard cadmium as a mutagen. In addition, the quantitative risk assessment was recalculated according to SAB's recommendation.

Unfortunately, the SAB's additional recommendations were not included in the final document. It is interesting to note that in their letter to the EPA, they criticized the EPA Cancer Assessment Group for not including the recommendations they made on the previous draft. This is not to say that the SAB's comments fell on deaf ears. Indeed, Dr. Thun almost immediately went about collecting more data in an effort to resolve the confounding effects of arsenic exposure and smoking among his original cohort. Rather than stating this, the final document repeatedly argues that the Thun analysis adequately addressed these confounding variables despite the absence of new evidence.

Since the final document was published, Dr. George Kazantzis did a case control study for long cancer as part of a recently completed cohort mortality study of 6,995 male cadmium workers (Appendix D). This case control study was done in response to the finding of an excess risk of lung cancer in the low exposure group of this cohort. Dr. Kazantzis found that this excess risk of lung cancer was not due to cadmium, nor was the excess risk of bronchitis found in the medium exposure group.

In addition, the Fraunhofer Institute has begun a long-term inhalation study with cadmium which is a follow-up to the Takenaka study. In order to confirm its original findings, hamsters and mice will be exposed to four different cadmium compounds, including cadmium oxide. This study should be completed sometime in late 1986.

Another reanalysis of the ASARCO cohort is presently being conducted by Dr. Steven Lamm of CEOH in Washington, D.C.. Dr. Lamm's preliminary analysis shows that arsenic exposure and smoking could have caused the excess of lung cancer deaths seen in this cohort.

According to Dr. Lamm, plant history indicates three industrial eras with respect to arsenic at this work site. Prior to 1926, the arsenic plant on site was actively refining the arsenic trioxide, but crude arsenic was only stockpiled after 1940, when the feedstock arsenic content dropped to about 1%.

Analysis of cohorts by date of hire, rather than by dates of employment, is necessary to separate the effects from each exposure period. Little industrial hygiene data preceeds the 1950's. Analysis of the mortality data indicates a marked lung cancer risk for workers hired prior to 1926 (and working through 1940), a moderate excess lung cancer risk for workers hired between 1926 and 1940 (and working through 1940), and no excess lung cancer risk for those hired in 1940 or later. These data would suggest that arsenic exposure might be the major determinant of risk.

With regard to smoking, histories of smoking habits for workers from fifty years ago cannot be obtained. Adjustments of expected lung cancer risk for missing smoking information is generally based on assumptions of risk as a function of pack-years of exposures. But, pack-years of exposure assumes linerity in risk for both intensity of smoking and duration of smoking, while epidemiological analysis indicates that duration of smoking is a four order risk

factor. Methodology for adjusting expected risks for duration of smoking history need to be developed. Dr. Lamm has begun to assess the effects of arsenic exposure and smoking for this cohort. The results of this analysis will be presented at the International Cadmium Conference to be held in San Francisco, February 4-6, 1986.

In an effort to resolve these questions, the Cadmium Council is among the sponsors of the International Cadmium Conference and a workshop chaired by Sir Richard Doll specifically on cadmium and cancer. Sir Richard Doll, one of the most outstanding epidemiologists in the world, stated in a recent publication entitled "Occupational Cancer: Problems in Interpreting Human Evidence" that in his view, cadmium should not be regarded as a human carcinogen with reference to prostatic cancer (Appendix E).

According to Sir Doll:

> "It must be remembered too, that when an unexpected finding is observed and further studies are made to check it, the first set of data must be regarded as hypothesis-forming and excluded from the subsequent analysis. Failure to remember this led the members of a recent INTERNATIONAL WORKSHOP ON THE CARCINOGENICITY OF METALS (1981) into error when they concluded, on the advice of a committee which I chaired, that 'exposure to cadmium had contributed to the development of prostatic cancer' in four series of cadmium workers. The data that were available to the committee are summarized in Table 4, and these results were assessed as being likely to turn up by

Table 4 Prostatic Cancer in Cadmium Workers: Evidence Available in 1981

Country	Number Observed	Expected	Characteristic
Great Britain	4	0.6	Cases
U.S.A.	4	1.2	Deaths
Sweden (1)	2	1.2	Cases
Sweden (2)	4	2.7	Cases
All countries	14	5.6	

chance along only twice in a thousand had the first British series been omitted, as it should have been, a further 10 cases would have been counted against 5.1 expected, giving a one-tailed P value of 0.04, the conclusion that cadmium contributed to the causation of prostatic cancer would have been, at the most, tentative, and the results of the recent large-scale studies of all men occupationally exposed to cadmium in the whole of England, which are summarized in Table 5, would not have come as a surprise."

As evidenced by this example, errors in analysis of epidemiological data can be made easily when statistical evidence is evaluated improperly. However, an error in judgement is assured when statistical evidence is ignored completely. The following statement from the draft document implicating a cause and effect relationship between cadmium and prostatic cancer which totally disavows the statistical evidence must be deleted:

"Because the human studies repeatedly find some elevation in risk, albeit a non-significant one, the staff of DHS does not believe that there is evidence to reject an effect of cadmium on prostatic cancer."

This statement is nothing more than an editorial comment. Something that should be left out of a scientific document.

As far as cadmium's ability to cause lung cancer, Sir Doll concluded that very careful evaluation is required before a decision about such an effect is reached.

Health criteria aside, another reason for not listing cadmium is because airborne exposure to cadmium is minimal. This is according to an EPA Office of Water publication entitled "Cadmium Contamination of the Environment: An Assessment of Nationwide Risk". In particular, the report found that zinc and cadmium smelting is no longer a major source because of tighter controls of other emissions.

Based on this, and other information presented before an EPA public hearing on the notice to list cadmium under section 112, the EPA has decided to extend the comment period for 90 days in order for additional information to be compiled. A copy of the hearing transcript is provided as Appendix F.

In view of the uncertainties which exist with regard to cadmium's ability to cause lung cancer and studies that have found emissions of cadmium into the environment to be minimal, it would appear that the listing of cadmium as a toxic air contaminant is unwarranted. The Council recommends that this be considered by the ARB and that no further action be taken at this time.

Giovina L. Leone, M.S.
Director, Environmental Health

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CIBA–GEIGY

February 3, 1986

Mr. William V. Loscutoff, Chief
Toxic Pollutants Branch
Air Resources Board
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Attention: CADMIUM

Dear Mr. Loscutoff:

CIBA-GEIGY Corporation appreciates the opportunity to comment on the DRAFT REPORT TO THE SCIENTIFIC REVIEW PANEL ON CADMIUM. We regret that it could not be supplied by January 17 but it is our understanding that you will accept and consider our comments.

CIBA-GEIGY handles cadmium chemicals in the workplace and produces cadmium pigments for the marketplace. We are interested in the proper and appropriate regulation of cadmium and its compounds for the protection of workers and the general public. Your draft document represents an excellent review of the available data as well as an attempt to rationalize the classification of cadmium as a toxic air contaminant for the general population. This rationalization is based on animal and human data purported to prove that cadmium, per se, is a carcinogen and a statistical extrapolation of these data to a risk for the population of California.

Before this process is finalized we have some comments on the data reviewed and assumptions made that should be considered. In addition, certain new data are made available for your evaluation.

The Takenaka, et al cadmium chloride inhalation study showed what could be interpreted as a dose-response in lung tumor incidence. However, this continuous 18-month dosing insult did not produce a dose-related effect on time of tumor occurrence. It took 27 months for a significant tumor response to reveal itself. Cadmium chloride is known to increase both lung epithelial permeability and the number of inflammatory cells in the lung. These effects, taken together with the chemical's continual presence in the lung without any possibility for lung clearance and repair probably drastically affected the study results. The EPA draft document even states that "the potential of $CdCl_2$ for altering the normal phagocytic activity could explain why the investigators were able to produce such a marked carcinogenic response."

This brings us to the issue of threshhold with respect to the potential of cadmium posing an inhalation carcinogenic risk to the general population at ambient air concentrations. The DHS staff has concluded that non-carcinogenic toxicities exhibit a threshhold and ambient airborne cadmium will not pose a significant hazard. Both Takenaka, et al and the EPA allude to a relationship between lung cadmium retention, alteration of normal phagocytic activity, alveolar damage with enhanced cell proliferation and the carcinogenic activity of cadmium chloride. Table 1 gives the change in lung tumor incidence with respect to decreasing dosage.

TABLE 1

Dosage (ug Cd/m^3)	Total Lung Tumors	Percentage Change From Next Higher Dose
50	25	-
25	20	20
12.5	6	70
0	0	100

As can be seen there are disproportionate changes with successive dose halving. It thus appears likely that lower dosages cause less lung damage (considered a threshhold event) and consequently less lung tumors. This would indicate that ambient airborne cadmium does not pose a carcinogenic risk to the general population and should not be classified as a toxic air contaminant. The Takenaka, et al study also provides evidence supporting the DHS staff in concluding that ambient airborne cadmium will not cause renal toxicity since the highest exposure level only resulted in a concentration of 34 ug Cd/g wet weight of kidney.

Data developed by Thun, et al was used by DHS staff to calculate the human risk of lung cancer. This epidemiology study has been commented upon by numerous groups (Metals Subcommittee of the Environmental Health Committee of EPA's Science Advisory Board, Cadmium Council and ASARCO). I have appended, rather than repeated, some of these comments. It is important to remember that this was an occupational, not ambient, exposure situation; levels were greater than 40 ug/m^3; working conditions varied over time with

decreasing cadmium exposures being evident; exposures to arsenic, lead and zinc also occurred; smoking habits could have accounted for half the increase; urine cadmium levels suggest a highly exposed population. Taken altogether this was a study that clearly demonstrated cadmium exposure (via urine) in a workforce that may not have consistently followed good hygiene practices and whose smoking habits were retroactively surmised. Workplace conditions which existed years ago can not be used to assess risk to the general population from ambient air exposure. It is of interest that Lauwerys, et al, (Toxicology Letters 23: 287-9, 1984) investigating the general populace living in industrial areas polluted by cadmium due to past emissions from non-ferrous metal industries found increased incidences of mortality related to nephritis and nephrosis but did not mention lung cancer even though the cause of death was obtained for each deceased person. This directly confirms the DHS staff position that renal effects are the most sensitive indicator and our position that extrapolation of lung cancer from worker exposure to the general population is not appropriate. Furthermore, no data from Japan suggests that non-occupational exposure to cadmium constitutes a carcinogenic hazard.

It is important to remember that all the inhalation epidemiology studies deal with exposures relating primarily and almost exclusively to battery production and ore smelting. These are hardly proper surrogates for the general population exposed to ambient air.

The lung is the most prevalent site of cancer in humans. Smoking is a recognized cause. The smoking histories in those studies purported to implicate cadmium as a lung carcinogen are either not available or are

sufficient to be considered a cause in themselves. Arsenic and nickel exposure also confound the issue. For instance, the EPA draft states the following about the Thun, et al study: "Of concern in this study is the possibility that the combined effect of increased cigarette smoking and exposure to arsenic might have served to produce the significant positive risk of lung cancer observed in this report. This possibility is all the more distinct because the risk of lung cancer in the study was not seen to be overwhelming. A subtle combination of factors such as the ones mentioned above could conceivably have served to produce the excess risks found, even though such an eventuality is unlikely. Thus, although this study cannot be said to be conclusive with respect to risks of lung cancer from exposure to cadmium, it constitutes the most clear-cut evidence yet leading to this conclusion." (Emphasis added.) Moreover, this statement appears to be at odds with a subsequent statement: "Strong evidence is available from the Thun et al. study that the significant two-fold excess risk of lung cancer seen in cadmium smelter workers is probably not due to the presence of arsenic in the plant or to increased smoking by such workers."

Any mathematically based risk assessment method dealing with a natural substance that ignores biological reality is flawed. In the case of cadmium, which is a substance that may be an essential trace element, biologic protective mechanisms (metallothionein production) exist to bind low levels and thus assist in preventing toxicity. To assume linear, no threshhold carcinogenic activity under these circumstances is biologically indefensible especially when a key inhalation study involves continuous

exposure over an eighteen month period under conditions which overwhelm the normal protective mechanisms in the lung. The body should be considered to have the capacity to repair any minimal DNA damage that might potentially occur from exposure of the general population to ambient levels of cadmium. The multistage model appears to assume that the likelihood of repair is not a dose-dependent process. The DHS staff alludes to these mechanisms though they end up stating that there is a finite probability that one molecule can cause a mutagenic or carcinogenic effect. Even if this were likely, some consideration should be given to how long it would take this one molecular hit to express itself as a cancer. If dose has any influence on the timing of this process and definitive cases take 20-40 years to be evident, then one molecule should induce a cancer long after the normal (or abnormal) life expectancy of an individual. The staff, in assuming no threshhold, states that there is always an excess cancer risk from exposure to any level of cadmium. By extension, this assumption would mean that any compound that has caused cancer in animals, without exception, will cause an excess cancer risk in people. This is not supported by the available evidence.

Another point worth covering is that all cadmium compounds are not alike with respect to toxicity or their absorption and distribution throughout the body. Table 2 compares the toxicity and absorption of various cadmium compounds. Note that cadmium sulfide, cadmium selenide, and cadmium sulphoselenide differ in acute toxicity from the other more soluble Cd compounds and that CdS has a slower lung absorption in the cat and dog. In addition, a study (Rusch, et al, submitted for publication and attached) was conducted comparing the acute toxicity, tissue distribution and rate of

elimination in rats following a 2-hour inhalation exposure to cadmium red, cadmium yellow, cadmium carbonate and cadmium fume. An equivalent dosage based on cadmium content was used for each test substance. There was no mortality in the control, cadmium red or cadmium yellow exposed groups. Mortality was 3/32 and 25/32 in the cadmium carbonate and cadmium fume exposed groups, respectively. Cadmium blood levels indicated that cadmium from the cadmium carbonate and fume was absorbed to a greater degree than cadmium from the red and yellow pigments. The majority of the elimination of cadmium following exposure to the two pigments was via the feces, with 80% being cleared within 24 hours. Elimination was slower following exposure to the carbonate and fume. The levels of cadmium in the liver and kidneys were many times higher following exposure to the carbonate and fume than following exposure to the red and yellow pigments. It is evident that cadmium compounds are not equivalent with respect to toxicity, absorption, distribution or excretion. Exposure to the two insoluble compounds, cadmium red and cadmium yellow did not produce mortality and resulted in more rapid elimination and far lower tissue levels of cadmium than was observed following exposure to the cadmium carbonate and cadmium fume.

A recent study by Oberdorster, et al (Toxicologist 5(1): 178, 1985) compared the toxicities of different Cd compounds to rat lungs. Cadmium sulfide had little if any effect on the measured parameters while $CdCl_2$ and CdO increased inflammatory cell influx and epithelial permeability.

Two other reports indicate the influence of solubility and physical state of cadmium compounds on toxicity and disposition. Aihara, et al

(Toxicology 36: 109-118, 1985) showed that a less soluble form of cadmium remained in the rat lung to a greater extent than a more soluble form with the latter increasingly being found over time in liver, kidney and intestine. Costa, et al (Cancer Research 42: 2757-2763, 1982) demonstrated that crystalline CdS was actively phagocytized by cells and induced morphologic transformation of Syrian hamster embryo cells while the amorphous form had significantly less activity at equivalent exposure concentrations and particle size.

The influence of metallothionein on cadmium has been investigated. Hart, et al (Toxicology 37: 171-179, 1985) exposed rats up to 30 times to a cadmium acetate aerosol via a nose only procedure at a concentration of 1.6 mg/m^3. Baseline cadmium lung levels rose 20-fold after 30 exposures while lung metallothionein increased 50-fold. Lee and Oberdorster (Toxicologist 5(1): 178, 1985) studied the fate of Cd-thionein in rat lung compared to cadmium chloride. They showed that $CdCl_2$ treated rats exhibited distinct clinical symptoms of general and lung toxicity which was not shown by Cd-thionein treated rats. Furthermore $CdCl_2$ was retained in the lung to a greater degree and was distributed to the liver while kidney was the primary organ with Cd-thionein. Takenaka, et al found relatively high lung cadmium levels considering that it was analyzed 13-months after the end of inhalation. This is especially true when comparing the Takenaka study to the work of Lee and Oberdorster, Rusch, et al, and Hart, et al. It is obvious that the Takenaka, et al study imposed a lung burden on the rats that bears no relationship to either larger amounts given for shorter periods or to ambient exposure of the general population.

In conclusion, we believe that the available animal and worker exposure data do not present a convincing picture that cadmium is a lung carcinogen presenting a risk to the general population of California through its presence in the ambient air. It should not be classified as a toxic air contaminant.

For your convenience, we are supplying copies of all references mentioned that are not on the literature list. In addition, the title page of a CEC document is included for completeness.

Very truly yours,

Martin E. Bernstein, Ph.D.
Manager, Toxicology

MEB:rp
Enclosure

TABLE 2

COMPARATIVE EFFECTS OF CADMIUM COMPOUNDS

Premise: All Cadmium compounds are not equivalent with respect to toxicity and absorption.

CADMIUM COMPOUND	SPECIES	EFFECTS
CdS	Rat	Oral LD_{50} = >5 g/kg
CdSe	Rat	Oral LD_{50} = >5 g/kg
$CdCl_2$	Rat	Oral LD_{50} = 88-302 mg/kg
$Cd(Ac)_2$	Rat	Oral LD_{50} = 333 mg/kg
$CdCO_3$	Rat	Oral LD_{50} = 438-659 mg/kg
$Cd(NO_3)_2$	Rat	Oral LD_{50} = 397 mg/kg
CdO	Rat	Oral LD_{50} = 72-296 mg/kg
$CdSO_4$	Rat	Oral LD_{50} = 357 mg/kg
CdO, $CdCl_2$, CdS	Dog	CdO and $CdCl_2$ are more readily absorbed.
CdO, CdS	Cat	CdO - Immediate lung effects as well as liver and kidney activity. CdS - Delayed effects (24-36 hrs.) limited to lung. Attributed to mechanical effect of blocking passageways due to insolubility and slow absorption.
CdO	Mice	Acute Oral LD_{50} = 72 mg/kg
$CdSO_4$	Mice	Acute Oral LD_{50} = 88 mg/kg
$CdCl_2$	Mice	Acute Oral LD_{50} = 93.7 mg/kg
$Cd(NO_3)_2$	Mice	Acute Oral LD_{50} = 100 mg/kg
CdS	Mice	Acute Oral LD_{50} = 1166 mg/kg
CdS-CdSe	Mice	Acute Oral LD_{50} = 2425 mg/kg

CalMat Co

CC FLAIR DRIVE/P O BOX 5210/EL MONTE, CALIFORNIA 91734-1210/(818) 307-8933

February 12, 1986

Mr. Richard Bode
ARB/Scientific Review Panel
1800 15th Street
P.O.Box 2815
Sacramento, CA 95812

Re: Report to the Scientific Review Panel on Cadmium

Dear Mr. Bode:

On behalf of our California Portland Cement Company subsidiary, I wish to comment upon the estimated cadmium emissions from portland cement manufacturing in California, as set forth in the January 1986 "Report to the Scientific Review Panel on Cadmium". I unfortunately did not receive this Report until February 6; after the February 5 deadline for submitting public comments. However, because the Cd emissions estimate in the Report appears to be overestimated by at least two orders of magnitude, I submit the following in the anticipation that corrections can be made prior to the ARB hearing on listing Cd as a toxic air contaminant.

On Table III, "Overview and Recommendation" (p.7), and Table II-1 "Sources of Atmospheric Cadmium" (p.II-5), the 1981 estimated emissions of Cd from cement manufacturing are listed as 6.5 tons/year. Calculations of this emission rate are presented in Appendix C (page C-4). An analysis of these calculations follows:

1. California Cement Production in 1981

The report states that 2.93×10^7 tons of cement were produced in 1981. This is incorrect and overstates the production by a factor of 3.7. Attached is the U. S. Bureau of Mines "Mineral Industry Survey, Cement Annual Advance Summary", July 15, 1982. Table 2 (p.4) lists the 1981 combined Northern and Southern California cement production as 7,878,000 tons.

For the purposes of estimating emissions, however, clinker production is relevant. Portland cement clinker is the intermediate material produced in the rotary kiln - the equipment from which the emissions in question emanate. Portland cement is manu-

factured by intergrinding the clinker with approximately 5% gypsum. Table 3 (p.5) of the USBM report lists the 1981 combined Northern and Southern California clinker production as 7,719,000 tons.

2. Tons of Feed Material

Approximately 1.6 tons of feed material to the rotary kiln is needed to produce one ton of clinker (not cement, as stated in the report). Thus, the total tons of kiln feed used in 1981 to produce clinker, by both wet and dry process kilns, was

$$1.6 * 7.72 \times 10^6 = 12.4 \times 10^6 \text{ tons kiln feed}$$

3. Total Kiln Particulate Emissions

All rotary kilns in California, wet or dry, are equipped with fabric filter baghouses or electrostatic precipitators to remove particulates from the kiln exhaust gases. Although I cannot provide appropriate documentation, it is conservative to assume, on a statewide average basis, that total particulate emissions from these control devices comply with the U.S.EPA Standards of Performance for New Stationary Sources, Subpart F, Portland Cement Plants. The relevant standard for rotary kilns (40CFR 60.62(a)(1)) limits total particulate emissions to 0.3 lb per ton of kiln feed. Thus, total 1981 particulate emissions from rotary kilns in California are estimated to be:

$$12.4 \times 10^6 \text{ tons kiln feed} * \frac{0.3 \text{ lb particulate}}{\text{ton kiln feed}} = 3.71 \times 10^6 \text{ particula}$$

4. Total kiln Cadmium Emissions

Similar to the methodology used by the CARB/DHS staffs for the Chromium toxic emissions report, it is appropriate to assume that the concentration of Cadmium in the rotary kiln baghouse/ESP particulate emissions is equal to the Cd concentration in the dust removed by these control devices (there are no data, of which I am aware, on the Cd concentration in the directly emitted particulate). Attached is a copy of the US Bureau of Mines report "Charterization of U.S. Cement Kiln Dust" (IC8885, 1982) by Haynes and Kramer. As part of this study, 113 samples of kiln dust from 102 U.S. plants (11 in California) were analyzed for trace element concentrations.

The trace element concentrations in the 113 individual kiln dust samples are listed in Table 7 (pp.13-15). As the eleven samples from California cement plants are not separately identified, the the concentration summary in Table 8 (p.16) must be used. For Cadmium, the mean concentration is 21 μg/g, or 21 ppm by weight.

Using this Cd concentration and the total kiln particulate emissions, the 1981 Cd emissions from cement manufacturing are estimated to be:

$$\frac{21 \text{ parts Cd}}{10^6 \text{ parts particulates}} * \frac{3.71 \times 10^6 \text{ lb particulate}}{\text{year}} * \frac{\text{ton}}{2000 \text{ lb}}$$

$$= \underline{\underline{0.039 \text{ ton Cd/yr}}}$$

Please let me know if you or the relevant staff representatives have any questions regarding these calculations. As part of the California cement manufacturing industry, we feel that it is most important that the toxic air contaminant report for Cadmium, as well as the forthcoming trace elements, reflect the best stationary source emissions estimates.

Sincerely,

Dr. David S. Cahn
Vice President-Regulatory Matters

Attachments

cc: P. Hawkins

IC 8885

Bureau of Mines Information Circular/1982

Characterization of U.S. Cement Kiln Dust

By Benjamin W. Haynes and Gary W. Kramer

UNITED STATES DEPARTMENT OF THE INTERIOR

MINERAL INDUSTRY SURVEYS

U. S. DEPARTMENT OF THE INTERIOR
BUREAU OF MINES
WASHINGTON, D.C. 20241

James G. Watt, Secretary — Robert C. Horton, Director

For information call Sandra T. Absalom,
cement specialist, or
Riena M. Lacroix, statistical assistant,
Telephone: (202) 634-1184

Cement, Annual Advance Summary

CEMENT IN 1981

U.S. cement consumption and production slumped in 1981 to the lowest levels since 1975, according to the Bureau of Mines, U.S. Department of the Interior. Cement demand, which declined for the second successive year, reflected reduced activity in the construction industry and general weakness in the U.S. economy. For example, total value of construction, in terms of constant (1977) dollars, decreased 3.5% to $155 billion, according to data published by the U.S. Department of Commerce. Housing starts decreased 16% to 1.1 million units.

Imports, a sensitive indicator of domestic cement demand, declined 24% to 4 million tons, and accounted for 5% of consumption, compared with 7% in 1980. Clinker imports were 31% of the total, compared with 36% in 1980. In a display of optimism for recovery in cement demand, several terminals for transshipment of imported cement began operations in California, Maine, and New York.

Shipments of portland and masonry cement from U.S. plants, excluding Puerto Rico, at 71.7 million tons, were 6% less than 1980 shipments and 16% less than 1979 shipments. No regional shortages occurred during 1981. Shipments decreased by at least 5% to all geographical regions except New England (up 1%), and the West South Central and Mountain regions (up 2% each). Shipments declined most severely to the East North Central (down 13%) and Pacific regions (down 12%).

Two new plants in Alabama and Utah collectively added more than 2 million tons per year to domestic cement production capacity in 1981. Seven other plants completed modernization programs that added approximately 3.5 million tons to U.S capacity. Most of these plant expansions occurred in California, and all of them were west of the Mississippi River.

Prepared in the Division of Industrial Minerals, July 15, 1982.

CIBA-GEIGY Corporation
Ardsley, New York 10502-2699
Telephone 914 478 3131

CIBA-GEIGY

June 18, 1986

Mr. Cliff Popejoy
California Air Resources Board
1102 Q Street
P. O. Box 2815
Sacramento, California 95812

Re: Cadmium

Dear Mr. Popejoy:

Enclosed, as discussed, is a toxicology report on studies in progress on various cadmium compounds. These long term rodent inhalation experiments show that different cadmium compounds exhibit dissimilar toxicity and distribution patterns, a conclusion that can be demonstrated by comparing the groups with similar exposure schedules.

Thus, hamsters exposed to cadmium oxide for 49 weeks at a concentration of 90 ug/m^3 showed a similar mortality to those exposed to cadmium sulfide pigment for 44 weeks at 1000 ug/m^3, a dose which was approximately 10 times greater.

Additionally, the distribution patterns in these two groups also showed differences between cadmium oxide and cadmium sulfide. Analysis of lung concentrations revealed that the cadmium sulfide exposed animals had about 15 times more cadmium present than the cadmium oxide exposed animals but similar kidney levels. This could indicate that increased lung levels of insoluble cadmium sulfide pigment are excreted via the gastro-intestinal tract rather than being absorbed into the circulation and distributed to the kidneys.

Furthermore, the cadmium sulfide exposed hamsters did not have lung edema or proteinosis which was seen in hamsters and mice exposed to lower concentrations of cadmium oxide for shorter periods of time. In addition, the cadmium sulfide hamsters had a lower incidence of bronchio-alveolar hyperplasia, lung cholesterol crystal deposits and fibrosis when the differences in concentration and exposure time are taken into account.

According to Dr. Heinrich, no cadmium-related carcinogenic effects have been observed in any of these experiments as of March, 1986. I will keep you informed of any additional information on these studies.

Yours truly,

Martin E. Bernstein, Ph.D
Manager, Toxicology
Safety, Health & Ecology

pop686/gm
Enc.

Inhalation Experiments in Rodents for Testing the Carcinogenicity of Cadmium Compounds

U. Heinrich, R. Fuhst, H. König, L. Peters, F. Pott, S. Takenaka
Fraunhofer Institut für Toxikologie und Aerosolforschung
D-3000 Hannover 61, Nikolai-Fuchs-Str. 1, FRG

Society of Toxicology, 25th Anniversary Meeting, March 3-7, 1986, New Orleans, Louisiana
Poster Session

inhalation of 12.5, 25 and 50ug Cadmium/m³ as $CdCl_2$ for about 150 hrs/week for 18 months induced lung carcinomas in rats (Takenaka et al. 1983). Therefore the carcinogenic effect of other Cadmium compounds and the susceptibility of other species should be investigated.

In this ongoing experiment male and female Syrian golden hamsters and female mice (NMRI) are exposed to aerosols of 4 different Cadmium compounds on 5 days/week, for 19 hrs/day or 8 hrs/day for 12-18 months. After termination of the exposure the animals are kept in clean air for another 6-12 months. The Cd-exposure is terminated prematurely if there is a substantial loss of body weight or increased mortality.

The Cd-aerosols are generated by atomizing $CdCl_2$ and $CdSO_4$ solutions and by nebulizing CdS suspensions. CdO dust aerosols are produced by atomizing Cd-acetate solutions with subsequent pyrolization of the Cd-aerosol at 750°C. The CdO fumes are generated by evaporation and oxidation of metallic Cd from Cd electrodes in an electric arc.

The particle size (mass) distribution is measured by a 8-stage cascade impactor. The mass median aerodynamic diameter of the aerosols is 0.2 - 0.6um.

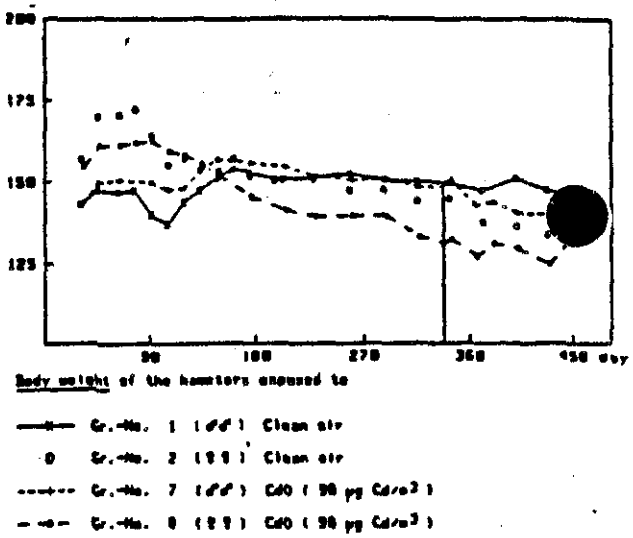
The Cd-concentration in the horizontal flow exposure chambers is determined daily by analyzing filter samples.

At the end of the experiment a comprehensive histopathological examination will be performed and the Cd content of lung, liver and kidney will be determined.
Some preliminary results are reported.

Experimental Plan

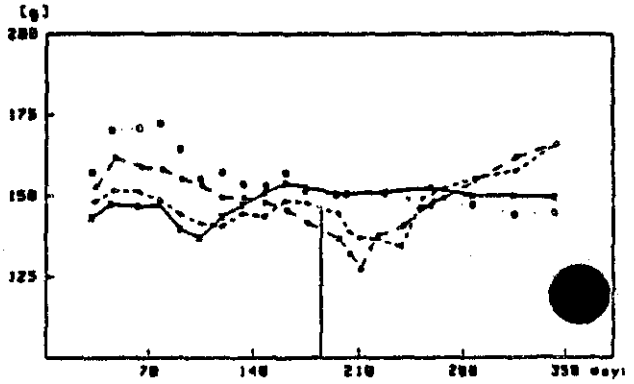
Substance-Concentration (ug Cd/m³)	Exposure Time (hrs/day)	Exposure Time (weeks) hamsters/mice	Experimental Time (weeks) hamsters ♂ / ♀ / mice ♀
clean air	-	- / -	+ / 85 / +
clean air	-	- / -	+ / 76 / +
clean air	-	- / -	+ / + / +
clean air	-	- / -	+ / + / +
$CdCl_2$-30	19	+ / +	+ / + / +
$CdCl_2$-90	19	59 / 42	+ / 76 / 81
$CdSO_4$-30	19	+ / +	+ / + / +
$CdSO_4$-90	19	60 / 42	+ / 81 / +
CdS-90	19	+ / +	+ / + / +
CdS-270	8	26 / 26	+ / + / +
CdS-270	19	60 / 59	70 / 64 / +
CdS-1000	19	44 / 41	59 / 60 / 70
CdO-10	19	+ / +	+ / + / +
CdO-30	19	59 / 59	+ / 85 / +
CdO-90	8	+ / +	+ / + / +
CdO-90	19	52 / 52	73 / 68 / 33
CdO-270	8	+ / +	+ / + / +
CdO-270	19	26 / 11	51 / 51 / 81
CdO-fume-10	19	58 / 58	+ / 79 / +
CdO-fume-30	19	52 / 52	+ / + / +
CdO-fume-90	8	+ / +	+ / + / +

n = 24 hamsters ♂, 24 hamsters ♀, 48 mice ♀
○ = still in progress



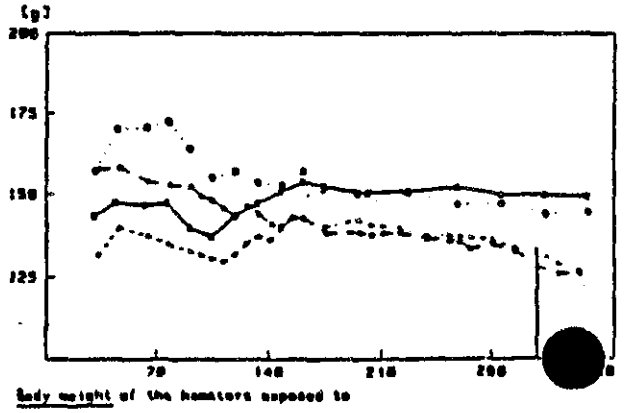
Body weight of the hamsters exposed to

—x— Gr.-No. 1 (♂♂) Clean air
-0- Gr.-No. 2 (♀♀) Clean air
---+--- Gr.-No. 7 (♂♂) CdO (90 µg Cd/m³)
—•— Gr.-No. 8 (♀♀) CdO (90 µg Cd/m³)



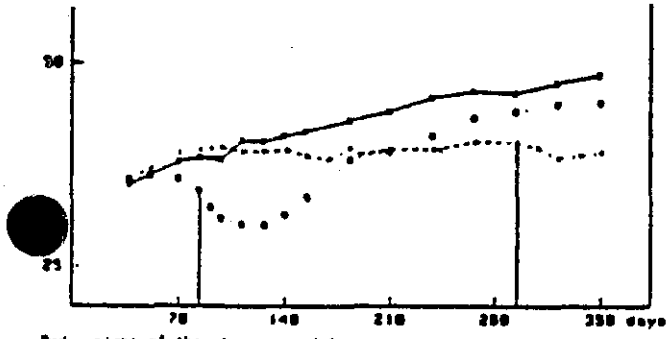
Body weight of the hamsters exposed to

—x— Gr.-No. 1 (♂♂) Clean air
-0- Gr.-No. 2 (♀♀) Clean air
---•--- Gr.-No. 11 (♂♂) CdO (270 µg Cd/m³)
—•— Gr.-No. 12 (♀♀) CdO (270 µg Cd/m³)



Body weight of the hamsters exposed to

—x— Gr.-No. 1 (♂♂) Clean air
-0- Gr.-No. 2 (♀♀) Clean air
---+--- Gr.-No. 17 (♂♂) CdS (1000 µg Cd/m³)
—•— Gr.-No. 18 (♀♀) CdS (1000 µg Cd/m³)



Body weight of the mice exposed to

—●— Gr.-No. 18 (♀♀) Clean air

0 Gr.-No. 23 (♀♀) CdO (270 µg Cd/m³)

------ Gr.-No. 27 (♀♀) CdS (1000 µg Cd/m³)

Body Weight Development

-------- End of Exposure

Cadmium Content of Mouse Lung, Liver and Kidney at the End of the Experimental Time (Exposure + Clean Air Time)

Exposure Concentration	Exposure Time (Weeks)	Clean Air Time (Weeks)	µgCd/g wet Weight		
			Lung	Liver	Kidney
CdO 270µgCd/m³	11	51	15.5 ± 7.9	7.2 ± 2.4	66.3 ± 19.9
CdS 1000µgCd/m³	41	29 - 30	238 ± 138	29.1 ± 6.8	199 ± 76

Cadmium Content of Hamster Lung, Liver and Kidney at the End of the Experimental Time (Exposure + Clean Air Time)

Exposure Concentration	Exposure Time (Weeks)	Clean Air Time (Weeks)	µg Cd/g wet Weight		
			Lung	Liver	Kidney
CdO 90 µgCd/m³	49	19 (♂)	38.5 ± 6.5	31.8 ± 8.4	25.3 ± 6.2
		49 (♂)	16.7 ± 3.5	26.1 ± 9.1	46.3 ± 21.2
		16 (♀)	31.5 ± 6.8	10.6 ± 2.5	44.5 ± 17.3
CdO 270µgCd/m³	28	25 (♂)	27.7 ± 4.8	22.1 ± 5.9	72.9 ± 18.7
		25 (♀)	28.8 ± 3.2	16.7 ± 4.1	60.4 ± 25.3
CdS 270µgCd/m³	60	7-10 (♂)	217 ± 39	19.1 ± 3.5	70.5 ± 23.5
		2-4 (♀)	214 ± 31	14.7 ± 1.9	61.9 ± 23.5
CdS 1000µgCd/m³	44	11-15 (♂)	542 ± 136	502 ± 28.8	28.4 ± 9.3
		14-17 (♀)	540 ± 77	30.5 ± 7.5	55.7 ± 24.2

Mortality Rate after Termination of Cd Exposure

Exposure Concentration	Exposure Time (Weeks)	Mortality		
		Exposed	Controls	
CdO 90 µgCd/m³	49 (♂)	12 %	0 %	Hamsters
	49 (♀)	21 %	8 %	
CdO 270 µgCd/m³	28 (♂)	8 %	0 %	
	28 (♀)	6 %	0 %	
CdS 270 µgCd/m³	60 (♂)	25 %	8 %	
	60 (♀)	79 %	29 %	
CdS 1000 µgCd/m³	44 (♂)	17 %	0 %	
	44 (♀)	21 %	8 %	
CdS 1000 µgCd/m³	41 (♀)	38 %	6 %	Mice
CdO 270 µgCd/m³	11 (♀)	0 %	0 %	

Even the exposure of hamsters to only 90ug Cd/m³ in CdO for 19 hrs/day caused an increased mortality after an exposure time of less than 1 year.

Cadmium Content of Hamster Kidney 1 - 4 Weeks after Termination of Exposure

Exposure Concentration	Exposure Time (Weeks)	µgCd/g Wet Weight	
		♂	♀
CdO, 90ugCd/m³	49	64.4 ± 21.6	26.7 ± 10.7
CdO, 270 µgCd/m³	28	78.4 ± 19.8	85.7 ± 24.5
CdS, 270 µgCd/m³	60	77.1 ± 10.9	43.2 ± 24.3
CdS, 1000 µgCd/m³	44	74.4 ± 30.2	24.9 ± 15.5

Due to very low solubility of CdS, there was no major difference in the kidney Cd-content of hamsters exposed to 90ug Cd in CdO or 1000ug Cd in CdS (Tab.7).

Compared to the CdO group the content of the lungs of the CdS exposed animals at the end of the experiment was about 15 times higher (Tab.8).

Even 51 weeks after termination of the exposure to 270ug Cd in CdO (11weeks), the Cd-content in the mouse lung was still 16µg/g w.wt. (Tab.9).

The Cd-content of the various organs of control animals was far below 1µg/g w.wt.

The Cd-concentration was determined on a Perkin-Elmer 2380 atomic absorption spectrophotometer equipped with an air-acetylene burner. The tissue samples (0.25g) were digested with nitric acid under pressure at 160°C.

Preliminary Histopathological Findings

a) Mice, 270ug Cd/m³ in CdO, 11 Weeks of Exposure + 51 Weeks Clean Air.

Lung:	Incidence
histiocytosis (foamy macrophages)	71 %
oedema/proteinosis	39 %
cholesterol crystals	50 %
thickened septa (fibrosis)	61 %

Kidneys, Liver: no exposure related changes.

b) Hamsters, 270ug Cd/m³ in CdO, 26 Weeks of Exposure + 25 Weeks Clean Air.

Lung:	Incidence ♂	♀
histiocytosis (foamy macrophages)	100 %	94 %
bronchio-alveolar hyperplasia	73 %	83 %
oedema/proteinosis	63 %	34 %
cholesterol crystals	50 %	52 %
thickened septa (fibrosis)	43 %	28 %
Kidneys:		
nephrosis/amyloidnephrosis (probably not Cd induced)	60 %	60 %

Liver: no exposure related changes.

c) Hamsters, 1000ug Cd/m³ in CdS, 44 Weeks of Exposure + 14 Weeks Clean Air.

Lung:	Incidence ♂	♀
histiocytosis (foamy macrophages)	100 %	100 %
bronchio-alveolar hyperplasia	43 %	65 %
oedema/proteinosis	0 %	0 %
cholesterol crystals	19 %	30 %
thickened septa (fibrosis)	24 %	48 %
Kidneys:		
nephrosis/amyloidnephrosis (probably not Cd induced)	76 %	78 %

Liver: no exposure related changes.

Conclusions:

1) No bronchio-alveolar hyperplasia is found after 11 weeks of CdO exposure in mice but after 26 weeks of exposure in hamsters.

2) Oedema/proteinosis were not observed in CdS exposed hamsters.

California Council for Environmental and Economic Balance

1512 - 14th Street Sacramento CA 95814 • (916) 443-8252

August 20, 1986

Mr. William V. Loscutoff
Chief, Toxic Pollutants Branch
Air Resources Board
P.O. Box 2815
Sacramento, CA 95812

RE: Cadmium

Dear Mr. Loscutoff:

The Council has reviewed the revised draft health effects report on cadmium, and appreciates the opportunity to submit these brief comments on several important policy matters that are addressed in the report. We are concerned that the health effects assessment does not accurately reflect the range of risk that may be posed by cadmium, because Department of Health Services' staff has chosen to exclude the very real possibility that there may indeed be no risk at measured ambient concentrations.

We can understand the basis for incorporation of the worst case policy assumptions DHS uses to emphasize the maximum possible upper bound risk (although we believe that risk assessments should also present the "most likely" risk estimate). However, such emphasis should not exclude an objective presentation of the very real possibility that a threshold may exist at concentrations a thousand times higher than the highest average concentration reported in California. In its 1985 "Updated Mutagenicity and Carcinogenicty Assessment of Cadmium", EPA objectively presented the possibility that a threshold might exist, and indicated that under such a thresholod assumption, a constant lifetime exposure to 10 micrograms per cubic meter would produce zero risk.

While we recognize that the existence of a threshold cannot be proven or disproven, the Air Resources Board needs to know the relative weight of the evidence regarding the plausibility of such thresholds when it is faced with making risk management decisions. The report does not convey to decision makers the particularly high degree of uncertainty associated with the estimated risk for such low levels as

those measured in the state. Accordingly the Council recommends that the health effects assessment be revised to state that the risk is estimated to be zero to 12 cases per million persons exposed to 1 ng/m^3. We also recommend that all future risk assessments contain a similar objective presentation of the threshold model.

Sincerely,

Evelyn F. Heidelberg

Evelyn F. Heidelberg
Vice President

EFH:cpr

CIBA-GEIGY Corporation
Ardsley, New York 10502-2699
Telephone 914 478 3131

CIBA–GEIGY

August 18, 1986

Mr. William V. Loscutoff
Chief, Toxic Pollutants Branch
Air Resources Board
P.O. Box 2815
Sacramento, California 95812

RE: CADMIUM

Dear Mr. Loscutoff:

CIBA-GEIGY Corporation appreciates the opportunity to comment on the June, 1986 revisions to Part B of the ARB Report on Cadmium.

Your group has continued its rational approach for dealing with a difficult issue, namely, whether substances present in the ambient air present a risk for the population of California. Your conclusion that cadmium is a toxic air contaminant is based on a risk assessment made by extrapolating data from the Thun, et al. study which purportedly demonstrates a relationship between occupational cadmium exposure and an increased incidence of lung cancer. A number of assumptions and conclusions have been made in the assessment process that require comment.

1. Thun, et al. (1985).

This study forms the basis of your assessment. It is currently undergoing a more detailed review. This will be discussed at an upcoming symposium, chaired by Sir Richard Doll, dealing specifically with the adequacy of epidemiologic studies on cadmium to classify it as a carcinogen. We have learned that at least one person whose lung cancer was attributed to cadmium is also included in another study where his lung cancer has been attributed to asbestos. In addition, a previously unconsidered confounding variable is possible exposure to radon. The plant under investigation is located in Colorado. To my knowledge no radon measurements have ever been made either at the plant site or in the surrounding communities. Since radon can cause lung cancer, this is an important factor which should be clarified.

2. Threshold/Non-Threshold Concept.

This matter was discussed in our previous comments. It is of interest that your reviewers consider negative in vivo mutation studies as being insensitive tests as opposed to being indicative that the body can effectively handle small doses of cadmium; i.e., exhibit threshold characteristics, at concentrations that might be present in ambient air. In fact, the absence of a carcinogenic effect in the Thun study at the two lowest doses indicates that a threshold does exist even in the workplace and would exist for ambient air where exposure is a thousandfold less. According to the authors, "The excess of deaths from lung cancer was statistically significant only for the stratum of workers whose cumulative exposure to cadmium exceeded 2920 mg-days/m^3, the level corresponding to a 40-year exposure above the current OSHA limit (200 ug/m^3). Workers whose cumulative exposure was below the 40-year equivalent of the NIOSH recommended TWA of 40 ug/m^3 showed no excess of lung cancer deaths."

Support for the concept of a threshold is derived from two other facts. First of all, excess cadmium can stimulate metallothionein synthesis which is known to detoxify cadmium following continuous low level exposure (Webb, M. (1979) in "Metallothionein", Kagi & Nordberg, editors, pp 313-20). Secondly, it is known that zinc and cadmium interact and compete for protein and enzyme binding sites. Your own reviewers acknowledge that zinc can reverse and/or prevent cadmium toxicity. The Thun study demonstrated that a critical concentration of cadmium was achieved only with the high dose workers. This critical concentration or threshold was not reached with the low dose workers. It would similarly not be reached by the general population of California which is exposed to relatively low ambient air levels of cadmium and which has zinc available in food, ambient air and mineral supplements.

3. Other Considerations.

3.1 Ambient Air - Occupational Exposure Relationships.

The use of occupational health standards to obtain an ambient air level is controversial and not uniformly accepted. Calabrese (Regulatory Toxicology and Pharmacology 6: 55 - 9, 1986) has stated, however, that "the methodology of dividing the TLV by 420 is consistently more conservative or protective than that derived from actual data". The ACGIH TLV for cadmium is 50 ug/m^3; dividing by 420 gives a safe ambient air level of 120 ng/m^3. Adoption of this value would provide a 3-fold safety factor over the "hot spots" and an approximate 50-fold safety factor over average California ambient air.

3.2 Dose Rate - Total Dose

At least one carcinogenicity study compared the relative effects of dose rate versus total dose (Littlefield, N. A. and D. W. Gaylor, J. Toxicol. Envir. Health 15: 545 - 50, 1985). In this study, it was found that "when the total doses were similar, the higher dose rates for shorter time periods induced a higher prevalence of tumors. Those groups dosed at higher rates but for fewer months had a generally higher prevalence than those receiving similar total doses but at lower rates for more months".

Certain cadmium inhalation studies in the rat also show the influence of dose rate. Oldiges & Glaser (Trace Elements in Medicine 3: 72-5, 1986) administered cadmium oxide continuously to Wistar rats for 22 hours/day, 7 days a week for either 218 or 324 days at a concentration of 90 ug/m^3. Exposure had to be terminated at this point because 12/40 animals had died. In the context of the interaction between zinc and cadmium discussed earlier, it is of interest that this concentration of cadmium oxide did not cause any mortality in 40 rats exposed simultaneously to zinc oxide for 374 days. In contrast, in a study by Kaplan, Blackstone & Richdale (ERDA Symp. Ser. 42, 77-97, 1977), Sprague-Dawley rats tolerated exposure to cadmium oxide at a concentration of about 300 ug/m^3 for 7-8 hours/day, 5 days/week for 9-13 months without any reported mortalities.

3.3 Effect of Smoking

It is acknowledged that cigarette smoking can contribute to the body load of cadmium. Post, Johansson & Allenmark (Environ. Res. 34: 29-37, 1984) autopsied 5 male heavy smokers between 65 and 78 years of age within about 3 days postmortem. They measured cadmium levels and degree of protein binding in the lungs, liver and kidneys. They found that human lungs contain a low molecular weight protein which binds cadmium and which appears to be similar to that found in the liver and kidneys. A lesser degree of cadmium binding was seen in the lungs compared to liver and kidneys.

3.4 Extrapolation

The extrapolation of animal studies to estimate human risk requires sophisticated statistical procedures and many conservative biological assumptions. Therefore, the use of human data is always preferred in estimating human risk. Thus, it is of interest that methods for species extrapolation were used with the data from the Thun, et al. human epidemiology study, which demonstrated a purported effect group (high-dose), a no-effect group (low-dose), and an intermediate effect group (mid-dose). Extrapolation should not be necessary for an adequate human study which demonstrates a no-effect level, particularly at a dose many times higher than ambient air concentrations.

In summary, we have presented our rationale for not considering cadmium as a toxic pollutant at ambient concentrations. Our reasoning is based on the facts that data exist showing that human lung tissue contains a cadmium binding protein considered to be metallothionein. Metallothionein is known to detoxify cadmium at continuous low levels of exposure. Zinc can also reverse and/or prevent cadmium toxicity. Animal studies have clearly demonstrated that different responses to inhaled cadmium exist and are related to a concentration-time response. Human epidemiology studies have shown that a toxic dose rate is many orders of magnitude higher than what the general population of California could experience at ambient air levels of cadmium. We contend, therefore, that no basis exists for classifying cadmium as a toxic air contaminant at ambient air concentrations nor is there substantiation for being "unable to identify a level below which adverse health effects are not expected to occur."

I have enclosed one copy of each article mentioned.

Yours truly,

Martin E. Bernstein/dck

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Encs.

lortality Among a Cohort of U.S. Cadmium roduction Workers—an Update [1]

I [redacted]J. Thun, *M.D., M.S.*,[2] **Teresa M. Schnorr**, *Ph.D.*,[2] **Alexander Blair Smith**, *M.D., M.S.*,[2] [redacted]. Halperin, *M.D., M.P.H.*,[2] *and* **Richard A. Lemen**, *M.S.*[2,3]

BSTRACT—A previous retrospective mortality study of 292 U.S. dmium production workers employed for a minimum of 2 years owed increased mortality from respiratory and prostate cancer id from nonmalignant lung disease. To examine further the ortality experience of these workers, investigators from the ational Institute for Occupational Safety and Health extended the udy to include 602 white males with at least 6 months of oduction work in the same plant between 1940 and 1969. Vital atus was determined through 1978, which included the addition of years to the original follow-up. Cause-specific mortality rates for even causes of death potentially related to cadmium exposure ere compared between the overall cohort and U.S. white males nd between subgroups. Mortality from respiratory cancer and from onmalignant gastrointestinal disease was significantly greater mong the cadmium workers than would have been expected from I.S. rates. All deaths from lung cancer occurred among workers mployed for 2 or more years. A statistically significant dose-esponse relationship was observed between lung cancer mortality nd cumulative exposure to cadmium. A 50% increase in lung ancer mortality, which was not statistically significant, was bserved even among workers whose cumulative exposure to admium was between 41 and 200 $\mu g/m^3$ over 40 years. Since the re[redacted]us investigation, no new deaths from prostate cancer and no [redacted] deaths from nonmalignant respiratory disease have been obs[redacted]d.—*JNCI* 1985; 74:325-333.

In 1976, Lemen et al. (*1*) published the results of a study on cancer mortality among cadmium production workers at a U.S. cadmium recovery plant. Using national white male rates for comparison, Lemen et al. reported a statistically significant excess of deaths from respiratory cancer (Obs=12; SMR=235), from nonmalignant respiratory disease (Obs=8; SMR=159), and, among workers with 20 or more years since first employment, from prostate cancer (Obs=4; SMR=452). The Lemen study included only hourly workers employed for 2 or more years between January 1, 1940, and December 31, 1969, and followed these workers through 1978.

A number of previous epidemiologic and experimental studies had suggested that cadmium might cause cancer of the prostate. Two occupational reports (*2, 3*) described excess mortality from prostate cancer among cadmium workers at a small British alkaline battery plant. Cadmium, like zinc, is known to concentrate in the prostate gland (*4-5*). Numerous toxicologic studies (*6-13*) have shown that injection of cadmium metal or salts into laboratory rats produces sarcomas locally and more [redacted]nt interstitial cell tumors of the testes. On the basis [redacted]se findings, the IARC (*14*) concluded in 1976 that "occupational exposure to cadmium in some form (possibly the oxide) increases the risk of prostate cancer in man." Substantial controversy continues, however, and although several subsequent epidemiologic studies (*15-18*) have found increased mortality from prostate cancer among occupational groups, other studies (*19-21*) have not.

Still more controversial is the possible relationship between cadmium and lung cancer. At the time of the IARC working committee, only the Lemen et al. (*1*) study had found excess mortality from respiratory cancer. Interpretation of that study was complicated because some of the long-term workers in the cohort also had been exposed to arsenic during the 1920's when the plant functioned as an arsenic smelter. Concern about the potential carcinogenicity of cadmium to the lung has increased, however, due to recent animal data. Takenaka et al. (*22*) exposed rats continuously to cadmium chloride aerosol and found a dose-dependent increase in lung tumors at exposure levels well within the current occupational limit.

Because of continuing concern about the effects of chronic cadmium exposure on mortality, NIOSH has extended the follow-up of the cohort first described by Lemen et al. (*1*). The present report describes the mortality experience of the group through 5 additional years of observation, ending December 31, 1978. In

ABBREVIATIONS USED: CI=confidence interval; Exp=expected; HIS=Health Interview Survey; IARC=International Agency for Research on Cancer; ICD=International Classification of Disease; NIOSH=National Institute for Occupational Safety and Health; NMGID=nonmalignant gastrointestinal disease; Obs=observed; OSHA=Occupational Safety and Health Administration; PEL=permissible exposure limit; PY=person-years; PYAR=PY at risk of dying; SMR=standardized mortality ratio(s); SRR=standardized rate ratio(s); TWA=time-weighted average.

[1] Received April 16, 1984; accepted August 20, 1984.

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[3] We thank Dr. George Hutchison, Dr. Karl Shy, and Dr. Philip Enterline for their advice in the analysis and interpretation of the data, Dr. Thomas Smith for his guidance in estimating exposures, and Dr. Lynne Moody for her epidemiologic and editorial counsel. We also acknowledge the dedicated follow-up efforts of Mrs. Edith Dodd, Mrs. Clorinda Battaglia, Ms. Judy Edelbrock, Ms. Mary Hogan, and their staffs and the excellent assistance in manuscript preparation by Ms Fran Guerra.

addition, to allow for internal comparisons, the study population was expanded to include 257 workers with brief (6-23 mo) employment and more complete ascertainment of workers with 2 or more years of employment. The total study population includes 602 white males.

BACKGROUND

The industrial plant under study has refined cadmium metals and cadmium compounds since 1925. It functioned previously as an arsenic smelter from 1918 to 1925 and as a lead smelter from 1886 to 1918. Although some cadmium processing operations were begun prior to 1925, the primary function of the plant for more than 50 years has been to recover cadmium and a number of other trace metals from "bag house" dust, a by-product of lead smelting. The facility is unusual in having a prolonged period of operation, with workers exposed predominantly to cadmium.

The industrial process recently was described by Smith et al. (*23*). Cadmium enters production principally as cadmium oxide dust (agglomerated fume). In a series of 10 physically isolated work areas, it is roasted, mixed with acid to form a cake, calcined, dissolved in water, recovered electrolytically, and treated further to produce cadmium oxide, metal, or yellow cadmium pigment. Air-monitoring data collected by the company from the 1940's to the present show that exposures differ substantially among departments and over time. Exposures have decreased over time due to the introduction of ventilation controls and to a mandatory respirator program introduced in the 1940's. Smith et al. (*23*) estimated the inhalation exposures that occurred in various departments (table 1). These estimates were based upon historical area monitoring data, adjusted to reflect the actual exposures of workers wearing respirators (*24*). Area-sampling data were first adjusted to reflect personal sampling, based on the ratio between area samples and personal exposure measurements from 1973 to 1976. For those departments and calendar periods in which workers wore respirators, the estimates of personal exposure were divided by 3.9, the geometric mean respirator protection factor measured in a survey at this plant in 1976 (*24*).

Also reflecting exposure are measurements of urine cadmium which the company obtained periodically on production workers since 1948. Urine samples were analyzed by colorimetric extraction until 1966 and subsequently by atomic absorption spectroscopy. Company records contained urine cadmium measurements for 261 members (43%) of the present cohort. These data are absent or extremely sparse for workers who left employment before 1960 and are representative only of production workers employed beyond 1960. Text-figure 1 shows the distribution of the median urine cadmium levels. These urine levels suggest a highly exposed population. They provide an index of group exposure but cannot be used to measure individual exposure because of the small number of samples for most workers (median of 2 samples/person; range, 0-79).

Few data are available on exposures other than cadmium at the smelter. Small quantities of high-purity lead, arsenic, thallium, and indium are produced sporadically by a few individuals in separate buildings. Some arsenic is evolved during cadmium recovery. An industrial hygiene survey conducted by NIOSH in 1973 found 0.3 and 1.1 μg arsenic/m^3 in the pre-melt department and 1.4 μg arsenic/m^3 in the retort department (*1*). These levels are substantially below the current OSHA 10 μg/m^3 PEL time-weighted average.

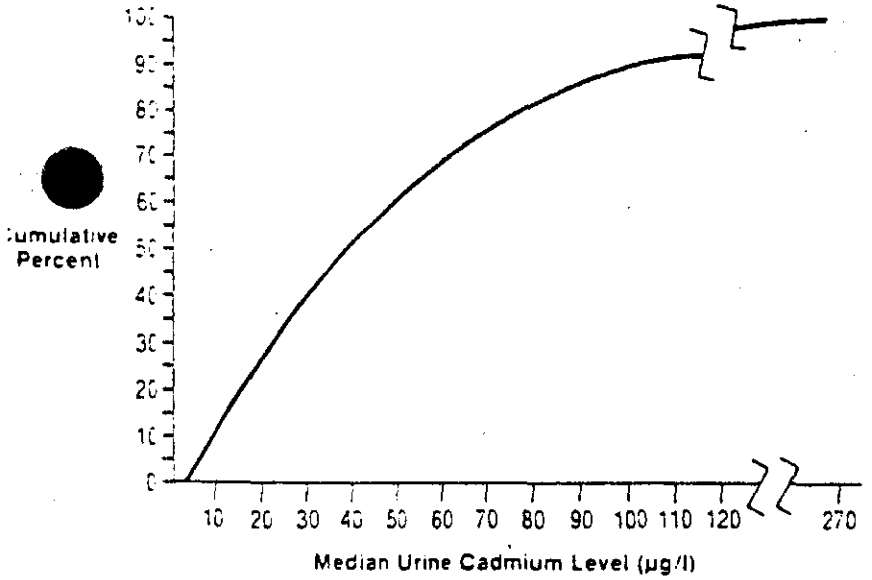
METHODS

The study population was defined from employment histories as recorded in the company personnel files. These records consist of a card for each employee and show the name, date of birth, social security number (since 1937), date of employment, date(s) of interruption of employment, and, in most cases, department or general work area for each period of employment. The records included retired and deceased as well as active employees. We enumerated all hourly employees and foremen who had worked a minimum of 6 months in a production area of the plant between January 1, 1940, and December 31, 1969. The requirement of production-area employment excluded several guards, office workers, and office area janitors who had been included in the Lemen et al. study (*1*). We also included production area foremen and a number of laborers whose records had been missing or whose employment histories had been inaccurately recorded and who thus had been omitted

TABLE 1—*Estimates of cadmium inhalation exposures, by plant department and time period*[a]

Time period	Cadmium inhalation exposure, mg·m^{-3}, in:									
	Plant departments:									Offices[c] and laboratories
	Sampling	Roaster	Mixing	Calcine	Solution	Tank house[b]	Foundry	Retort	Pigment	
Pre-1950	1.0	1.0	1.5	1.5	0.8	0.04	0.8	1.5	0.2	0.02
1950–54	0.6	0.6	0.4	1.5	0.8	0.04	0.1	0.2	0.2	0.01
1955–59	0.6	0.6	0.4	1.5	0.4	0.04	0.1	0.2	0.04	0.01
1960–64	0.6	0.6	0.4	0.4	0.4	0.02	0.1	0.2	0.04	0.007
1965–76	0.6	0.6	0.4	0.15	0.04	0.02	0.04	0.2	0.04	0.007

[a] Data from Smith et al. (*23*).
[b] Tank house estimates also were used for nonproduction plant departments that were not measured directly, e.g., the repair shop.
[c] Office estimates also were used for nonplant areas that were not measured directly, e.g., areas patrolled by the plant guard.



TEXT-FIGURE 1.—Cumulative distribution of median urine cadmium levels among 261 members of the cohort with at least one urine cadmium measurement. The median urine cadmium, in micrograms/liter, was computed for each worker for whom urine samples were available.

from the Lemen cohort. NIOSH identified the cohort jointly with a representative from the company and reviewed the list with senior union officials.

For each worker, cumulative exposure to cadmium was calculated according to length of employment and jobs within the plant. Because many of the personnel records specified general work categories rather than single departments, we categorized each period of a worker's employment into one of 7 broad job categories; e.g., category 1 included production work in any of 6 "high"-exposure departments, including sampling, roasting and bag house, mixing, calcine, foundry, and retort. Category 2 included production work in the solution, tank house, and pigment departments. The average exposure to airborne cadmium for each of these composite categories was calculated on the basis of the industrial hygiene data in table 1 (*23*), with each department contributing to a weighted average according to the proportion of workers usually employed there. Each worker's cumulative exposure over time was computed as the sum of the number of days worked in a given job category multiplied by the average inhalation exposure of that category for the relevant time period. Cumulative exposure was expressed in milligram days per cubic meter (mg-days/m^3).

The vital status of all workers in the cohort was determined as of December 31, 1978. Follow-up procedures used the records of the Social Security Administration, of the state vital statistics offices, and of the company and union and direct telephoning. Death certificates were obtained for persons known to be deceased and were coded by a qualified nosologist according to the protocol of the ICD revision in effect at the time of death. The codes were subsequently converted to the seventh revision codes for the analysis (*25*). Under the rules of this and subsequent revisions, cancer is coded as the underlying cause of death if the immediate cause of death is "unmistakably a direct sequel of" the malignant disease. Deceased workers for whom no death certificate has yet been located were assumed dead on the date specified by the reporting agency, with cause of death unknown. Persons lost to follow-up were assumed to be alive—which might possibly result in overestimation of cause-specific expected deaths.

The mortality experience of the cohort was analyzed with the use of a modified life-table system developed by NIOSH (*25*). In this system, a worker accumulates PYAR upon completion of the eligibility period (in this study, at 6 months of employment). The PYAR are specific for 5-year age groups, calendar periods, and years since first employment (latency). An expected number of deaths is calculated by multiplying U.S. white male death rates by the corresponding age and calendar-year PYAR categories. The resulting quantities are summed over all ages and years to obtain the total expected numbers. The observed numbers of cause-specific deaths are compared with the numbers expected. The ratio of observed-to-expected deaths multiplied by 100 is expressed as the SMR.

In the initial analysis, in which mortality in the cadmium workers was compared to that of the general U.S. white male population, the causes for which excess mortality or morbidity were observed in previous studies of cadmium workers were considered a priori to be of particular interest. Those of central concern included deaths from prostate and lung cancers (*1*, *20*) and from nonmalignant respiratory and renal diseases (*6*, *15*, *16*). Other conditions for which a priori concern has been raised include hypertension (*6*, *26*) and renal cancer (*27*). Mortality from NMGID also was examined because of the acute gastrointestinal toxicity of cadmium and because of reports of chronic gastritis and gastrointestinal ulceration (*28–30*). Although in each case cadmium is suspected of causing an excess of mortality, we present 95% CI, corresponding to a two-sided alpha level of 0.05, throughout this paper. Where the 95% CI includes the null but the 90% does not, we present both. CI were

TABLE 2.—*Vital status of white male cadmium production workers, by employment duration*

Worker status	Workers, No. (%), employed:		
	6–23 mo	2+ yr	Total
Alive	189 (74)	222 (64)	411 (69)
Dead	60 (23)	119 (35)	179 (29)
Lost to follow-up	8 (3)	4 (1)	12 (2)
Total	257	345	602

calculated with the use of Fisher's exact CI (if either the observed or expected was less than 10) or approximate CI (if observed or expected frequencies were 10 or more) (*31*).

For selected causes of death we examined mortality in relation to cumulative exposure to cadmium. For subgroup comparisons we used the directly standardized SRR as the measure of effect (*32*). To compute these, the age-specific and calendar time-specific rates of the subgroup were multiplied by the corresponding PYAR cells of the standard population—here the PYAR distribution of the overall cadmium cohort. The results were summed to yield the expected number of deaths that would occur in the overall cohort were the rates of the subgroup to apply. This total number of expected deaths was divided by the total number of PYAR in the overall cohort to yield a directly standardized mortality rate. The ratio of this rate to the standardized rate for the overall cohort, if U.S. age, sex, race, and calendar-period rates applied, yielded the SRR.

To analyze mortality by cumulative exposure, we chose the exposure categories a priori, on the basis of current or proposed regulatory standards and on the assumption that such standards are intended to protect a worker over a 40-year working lifetime; e.g., 40 years' exposure to cadmium at or below the current NIOSH proposed TWA of 40 $\mu g/m^3$ would result in a cumulative exposure of up to 584 mg-days/m^3. Forty years' exposure to cadmium at levels above the current NIOSH TWA, but within the current OSHA 200 $\mu g/m^3$ PEL, would result in a cumulative exposure of up to 2,920 mg-days/m^3.

RESULTS

Because of the small number of nonwhites and females (total = 13) in the cohort, we restricted the analysis to the 602 white males. Table 2 shows the vital status of these workers, by duration of employment, as of December 31, 1978. Of these, 411 were alive, 179 were dead, and 12 (2.0%) had unknown vital status; 43% had been employed for less than 2 years.

Text-figure 2 shows the distribution of the cohort by year of first employment. Two-thirds of the individuals had started work before 1949 and thus could be followed beyond 30 years. Nearly 83% had over 20 years of follow-up.

Table 3 compares the number of cause-specific deaths among the overall cohort with the number expected, based on U.S. rates. A deficit was observed in mortality from all causes (SMR = 95; 95% CI = 81–110), due to a deficit in diseases of the circulatory system (SMR = 65; 95% CI = 49–85). Significantly increased mortality was observed for respiratory cancer and NMGID. The excess of nonmalignant respiratory disease was not statistically significant in the overall cohort.

Twenty deaths were due to respiratory cancer, all among workers with over 2 years' employment and all due to cancers of the lung, trachea, and bronchus. Expected deaths were 11.43 in this more specific subgroup (ICD code 162–163), which was subsequently called lung cancer. Two of the deaths from lung cancer were initially miscoded as being due to other causes. Inasmuch as the immediate causes of these 2 deaths were unmistakably direct sequels of malignant conditions, the deaths were recoded to lung cancer in accordance with the rules of the ICD Seventh Revision. Analysis that excluded these cases yielded an SMR for lung cancer of 157 (18 Obs vs. 11.43 Exp; 95% CI = 93–249; 90% CI = 102–254).

TEXT-FIGURE 2.—Cumulative distribution by year of first employment for cadmium production workers included in cohort.

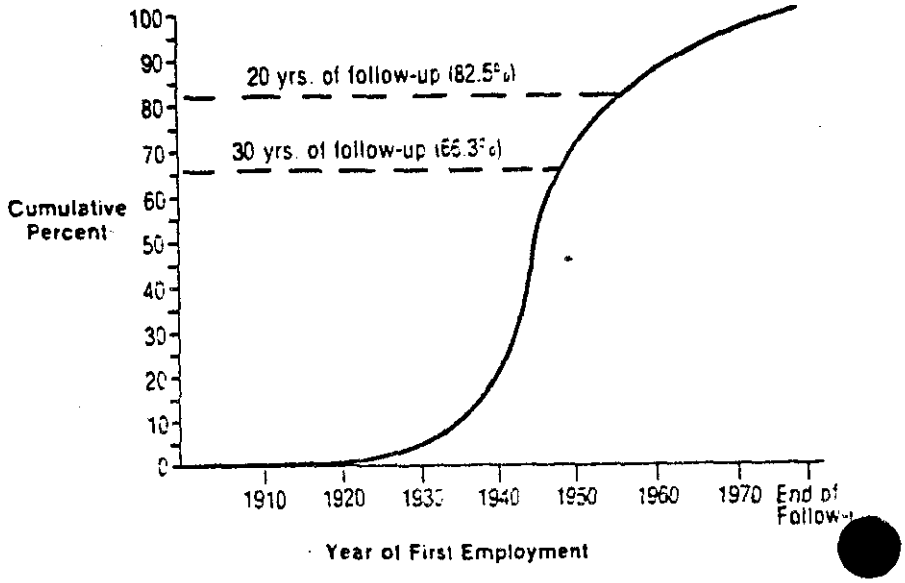


TABLE 3.—*Mortality from selected causes of death among white males with 6 or more months of cadmium production work: 1940–69*

Cause of death	ICD, 7th revision	No. of deaths		SMR	95% CI
		Obs	Exp		
Malignant neoplasm	140–199	41	36.46	112	81–153
Digestive system	150–159	7	10.85	65	26–133
Respiratory system	160–164	20	12.15	165	101–254
Genitourinary tract	177–182	6	4.45	135	49–293
Lymphatic and hematopoietic tissues	200–205	3	3.37	89	17–270
Other unspecified neoplasms		5	5.64	89	29–207
Diseases of the circulatory system: Heart disease	400–468	56	85.68	65	49–85
Nonmalignant respiratory diseases	470–493, 500–527	16	10.37	154	88–251
Acute infections, influenza, pneumonia	470–493	7	4.47	157	63–323
Other respiratory diseases	500–527	9	5.90	153	69–290
NMGID	540–543, 560–561, 570	9	2.35	383	175–727
All other causes	—	57	54.01	106	80–137
All causes of death	—	179	188.87	95	81–110

Of the 6 deaths from genitourinary cancer, 1 was due to renal cancer (vs. 0.92 Exp), 2 to cancers of the bladder and other urinary organs (vs. 1.10 Exp), and 3 to prostate cancer (vs. 2.20 Exp). No new deaths from prostate cancer were observed since the Lemen et al. report (*1*).

One of the original prostate cases was a plant guard who was excluded from this cohort because he had not worked 6 months in a production area. Another deceased worker had prostate cancer listed as a contributing cause of death but could not be included in this analysis because prostate cancer was not listed as the underlying cause of death. The remaining 3 deaths from prostate cancer had occurred among workers with 2 or more years of employment and 20 or more years of observation (vs. 1.41 Exp; SMR=213; 95% CI=44–622).

Sixteen deaths occurred due to nonmalignant respiratory disease; 7 of these involved workers employed for less than 2 years. The death certificates of 3 workers mentioned silicosis. Silica exposure may have occurred from work with refractory brick in furnace areas of the plant but is undocumented. One of the workers whose certificate mentioned advanced silicosis had been employed for only 1 year, suggesting that the exposure had occurred elsewhere.

We noted 9 deaths from NMGID, excluding cirrhosis. The death certificates of 6 of these suggested peptic ulcer disease. Most of the deaths from NMGID were of long-term employees, whereas 5 of the 6 deaths attributed to cirrhosis involved short-term workers.

No excesses were noted for deaths attributable to hypertension (3 Obs; 3.22 Exp) or to nonmalignant renal disease (1 Obs; 1.35 Exp). A single death certificate listed renal disease as the underlying cause of death [death had been due to acute nephritis (ICD code 590)], and 4 other certificates listed nonmalignant renal disease as a contributing cause of death. No comparison rates were available for analysis of these contributing causes of death.

Arsenic Exposure

Substantial arsenic exposure occurred throughout the plant during the years 1918–25 when the facility functioned as an arsenic smelter. Because arsenic is a known risk factor for lung cancer (*33*), we stratified the cohort into workers employed before and those first employed on or after January 1, 1926. We then compared mortality from lung cancer among each of these subgroups with that of U.S. white males (table 4). Lung cancer mortality was significantly elevated among persons hired prior to January 1, 1926. Among workers hired after that date, the excess of lung cancer deaths was statistically significant among workers employed for 2 or more years. When the 2 initially miscoded deaths from lung cancer are excluded from this analysis, mortality from lung cancer remains statistically above that expected both for workers hired prior to 1926 (Obs=3; Exp=0.56; 95% CI=110–1565) and for workers with 2 or more years' employment who had been hired after 1926 (Obs=15; Exp=7.0; 95% CI=120–353).

Mortality by Cumulative Exposure to Cadmium

Tables 5 and 6 present data on mortality from lung cancer and NMGID in relation to cumulative exposure to

TABLE 4.—*Mortality from lung cancer (ICD 162–163) in white male cadmium production workers, by date of hire*

Worker employment status	No. of deaths		SMR	95% CI
	Obs	Exp		
Hired prior to January 1, 1926	4	0.56	714	195–1829
Hired on or after January 1, 1926				
Overall cohort	16	10.87	147	84–239
≥2 years employment	16	7.00	229	131–371

cadmium. Only the 576 workers hired on or after January 1, 1926, are included in these analyses. Lung cancer mortality increased with increasing cumulative exposure to cadmium, and this trend was apparent both in the SRR and the SMR. A similar pattern was seen when the analysis was restricted to workers with 20 or more years since first exposure. The regression slope for the SRR for lung cancer (table 5) was 7.33×10^{-7} ($P=.0001$). The excess of deaths from lung cancer was statistically significant only for the stratum of workers whose cumulative exposure to cadmium exceeded 2,920 mg-days/m^3, the level corresponding to a 40-year exposure above the current OSHA limit (95% CI for the SMR = 113-577). In a separate analysis (not shown), workers whose cumulative exposure to cadmium ranged from 293 to 584 mg-days/m^3 showed an SMR for lung cancer of 100 and an SRR of 0.96. This level of cumulative exposure is equivalent to 40 years' exposure to airborne cadmium at levels between 21 and 40 μg/m^3. In contrast to its relationship with cumulative exposure, the excess of lung cancer mortality did not increase with length of employment beyond 2 years. Workers employed for 2-9 years, 10-19 years, and 20 or more years all showed approximately twice the number of deaths from lung cancer as expected from the U.S. rates.

Only 6 deaths from NMGID occurred among workers hired since 1926. A statistically significant upward trend was evident in the SRR when mortality from NMGID was analyzed by cumulative exposure (slope $=2.73\times10^{-7}$; $P=.014$). Because of the small number of cases of NMGID, these estimates are less stable than those for lung cancer. Three additional deaths from NMGID occurred among the 26 workers hired before 1926. If arsenic were unrelated to NMGID, these deaths would increase further the observed mortality in the high-exposure, long-term employment subgroup.

A similar analysis of deaths from nonmalignant respiratory disease was not performed, inasmuch as this study found no significant excess of deaths from this cause either in the overall cohort or among workers with 2 or more years of employment. An excess of deaths in this category was apparent, however, among workers employed for 6 months to 2 years (Obs = 8; Exp = 3.2; SMR = 249; 95% CI = 108-491). One of these deaths was attributable to silicosis.

TABLE 5.—*Lung cancer (ICD 162-163) mortality, by cumulative exposure to cadmium: White males hired on or after January 1, 1926*

Cumulative exposure, mg-days/m^3	40-yr TWA equivalent*	PYAR	No. of deaths	SMR	SRR
≤584	≤40 μg/m^3	7.005	2	53	0.48
585-2,920†	41-200 μg/m^3	5.825	7	152	1.55
≥2,921	≥200 μg/m^3	2.214	7	280	3.45
U.S. white males		—	—	100	1.00

*The TWA that over a 40-year working lifetime would result in the indicated cumulative exposure.

†Exclusion of the single worker hired after 1926, whose death from lung cancer was initially miscoded, reduces the number of observed deaths in this stratum to 6 and the SRR to 1.34.

TABLE 6.—*NMGID (ICD 540-43, 560-61, and 570) mortality, by cumulative exposure to airborne cadmium: White males hired on or after January 1, 1926*

Cumulative exposure, mg-days/m^3	40-yr TWA equivalent*	PYAR	No. of deaths	SMR	SRR
≤584	≤40 μg/m^3	7.005	2	300	4.8
585-2,920	41-200 μg/m^3	5.825	1	112	1.0
≥2,921	≥200 μg/m^3	2.214	3	582	11.3
U.S. white males		—	—	100	1.00

*The TWA that over a 40-yr working lifetime would result in the indicated cumulative exposure.

DISCUSSION

The findings of principal interest in this study were the increased mortality from lung cancer among workers employed for 2 or more years and the dose-response relationship between lung cancer mortality and cumulative exposure to cadmium. The excess of malignant respiratory disease, noted previously in this cohort by Lemen et al. (*1*), has continued during the expanded observation period. Eight new deaths from lung cancer have been identified. The excess of deaths from respiratory cancer among workers with 2 or more years of employment continues to be statistically significant (new cases = 8; Exp = 2.94; SMR = 272; 95% CI = 117-536). Furthermore, because national death rates for respiratory cancer overestimate regional (State of Colorado or Denver County) rates by 10-25% (*34*), the measured excess of lung cancer deaths among longer-term employees probably underestimates the actual increase.

The observed excess of deaths from respiratory cancer could be due to a true causal relationship between cadmium and lung cancer, to bias (the effect of uncontrolled confounding), or to chance. Cigarette smoking and exposure to arsenic are two extraneous factors which, if uncontrolled in the analysis, could explain the findings. Although the tobacco smoking habits of these cadmium workers were not recorded at the time of employment, company representatives did collect information on past tobacco use by mailing a questionnaire to members of the cohort in 1982 (*35*). Interviews with approximately 70% of survivors or next of kin showed that 77.5% of those for whom information was gathered were current or former smokers. This prevalence of "ever smokers" resembles the 72.9% prevalence noted among U.S. white males, age 20 or over, in the 1965 HIS (*36*). The 1965 HIS is perhaps the best source of information on the smoking habits of the general population during the observation period of this study. Using the 1965 survey data, one can estimate the effect that disproportionately heavy smoking by the cadmium workers would have on lung cancer mortality relative to that of the general population. Computations developed by Axt (*37*) and Blair and Spiritas (*38*), combined with th

ta, show that even an assumed doubling of the oportion of heavy smokers will have only a small effect the rate ratio for lung cancer; e.g., if 40% of the dmium workers smoked more than 25 cigarettes/day, ed to 20% of the 1965 white male general on, the rate ratio would increase only 1.25-fold. hus cigarette smoking alone is unlikely to account for e twofold-to-threefold increase in deaths from lung ncer observed among workers in this cohort who had ad 2 or more years of employment.

Substantial and widespread arsenic exposure occurred ior to 1926 when the plant operated as an arsenic nelter. The rate of lung cancer mortality among the 26 orkers employed before 1926 was nearly six times the .S. rates. Even after 1925, a small and unspecified umber of workers occasionally processed arsenic in one ea of the plant. This was an intermittent operation, pparently staffed by workers from the roasting area, and sted into the 1930's. A second and continuing source of xposure involved workers in the sampling, mixing, asting, and calcine furnace areas of the plant who were xposed to arsenic contamination from the incoming ed material. Only six industrial hygiene measurements ere made in these areas before 1975. In 1950, airborne rsenic concentrations ranged from 300 to 700 $\mu g/m^3$ ear the roasting and calcine furnaces, the areas of ighest exposure. Measurements by the company and)SHA in 1979 show that arsenic exposures in these areas ad decreased to about 100 $\mu g/m^3$. Although air levels of rsenic in this confined area were still 10 times higher n the legal OSHA threshold limit value of 10 $\mu g/m^3$, personal exposures were lower due to respirator sage. One can estimate the number of lung cancer eaths potentially attributable to arsenic by assuming *a*) n average airborne arsenic exposure of 500 $\mu g/m^3$ in the "high-arsenic" work areas during the years of this study,) a respirator protection factor of 75% (similar to that ssumed for cadmium), and *c*) an estimated 20% of PY of xposure spent in high-arsenic jobs, an estimate based on ersonnel and biologic monitoring data. On the basis of hese assumptions, the average airborne arsenic exposure f persons in this study would have been 25 $\mu g/m^3$. nasmuch as the 576 workers hired after 1926 were mployed an average of 3 years, they acquired 1,728 PY of xposure to 25 $\mu g/m^3$. Such an exposure should result in o more than 0.77 lung cancers, on the basis of a risk ssessment model for arsenic developed by the OSHA 39).

Although the estimate of an average air exposure to rsenic of 25 $\mu g/m^3$ rests on several assumptions, it is more likely to overestimate than to underestimate actual xposures. Only a fraction of jobs in the high-arsenic areas involved exposures as high as those of the furnace areas. High-exposure jobs in the roaster area were frequently staffed by entry-level workers, many of whom worked less than 6 months. These very short-term workers with brief but high exposure were excluded from the mortality study, yet they were included in our estimate of 20% of PY of exposure spent in high-arsenic jobs. In addition, urinary arsenic levels measured on workers in the high arsenic areas from 1960 to 1980 averaged only 46 μg/liter, a level consistent with an average inhaled arsenic concentration of 14 $\mu g/m^3$ (*40*). Thus the assumption of an average inhaled concentration of 125 $\mu g/m^3$ (25% of 500 $\mu g/m^3$) over these years overestimates the actual exposures by ninefold, more than compensating for the unquantified higher exposures during the early years. Arsenic alone does not appear to explain the observed excess of deaths from lung cancer.

The central finding of the study was the observed dose-response relationship between mortality from lung cancer and cumulative exposure to cadmium. Previous epidemiologic studies of cadmium workers have had insufficient industrial hygiene data to estimate cumulative exposure. The strong dose-response pattern observed in this study is consistent with a causal relationship between cadmium and lung cancer. It also suggests that the current OSHA occupational standard, limiting exposure to cadmium dust to 200 $\mu g/m^3$, is inadequate to protect workers over a 40-year working lifetime. Workers whose cumulative exposure was below the 40-year equivalent of the NIOSH-recommended TWA of 40 $\mu g/m^3$ showed no excess of lung cancer deaths, whereas workers whose cumulative exposure was within the current OSHA limit but above the NIOSH recommended limit showed a 50% excess in lung cancer deaths.

The potential role of cadmium as a pulmonary carcinogen has gained biologic plausibility because of the experimental induction of lung cancer in rats exposed to cadmium chloride aerosol (*22*). Epidemiologic studies of mortality among cadmium workers in England and Sweden have, however, shown conflicting results. Sorahan and Waterhouse (*18*) found a statistically significant excess of deaths from respiratory cancer (Obs=89; Exp=70.2; SMR=127; 90% CI=106-151) in a cohort of 3,025 English nickel-cadmium battery workers. A subset of these workers had been included in the earlier studies of Potts (*2*) and Kipling and Waterhouse (*3*). Although the authors observed a positive association between death from respiratory cancer and cumulative duration of employment in jobs with high or moderate exposure to cadmium, they noted that these workers also were exposed potentially to oxyacetylene welding fumes and to nickel hydroxide dust. Holden (*17*) found a statistically significant excess of deaths from respiratory cancer (Obs=36; Exp=26.06; SMR=138; 95% CI=108-339) and from prostate cancer (Obs=8; Exp=3.00; SMR=267; 90% CI=115-525) among 624 cadmium "vicinity" workers but not among 347 workers employed directly in manufacturing cadmium copper alloys. The vicinity workers were also exposed to arsenic.

Armstrong and Kazantzis (*19*), excluding the cohorts studied by Sorahan and Waterhouse (*18*) and Holden (*17*), recently described mortality among workers enrolled in the registry of English cadmium workers. A small, statistically insignificant excess of deaths from respiratory cancer was evident in the overall cohort (Obs=199; Exp=185.6; SMR=107; 95% CI=92-122). This marginal excess is consistent with the results in our study, inasmuch as most of the workers in the Armstrong cohort

had only minimal exposure to cadmium. Less than 8% of the workers in the Armstrong cohort were classified as "ever highly exposed." High exposure was defined as having worked at least 1 year in a job that the authors judged would produce a urine cadmium level of at least 20 μg/liter following chronic exposure. In our cohort, 81% of workers for whom urine cadmium had been measured had a median urine cadmium of at least 20 μg/liter. Even among workers with less than 2 years of employment, approximately 30% had a median urine level of 20 μg/liter. One might argue that in each of the epidemiologic studies in which excess mortality from lung cancer was seen, other occupational exposures such as arsenic or nickel were present and could have contributed to the problem. Unfortunately, the published versions of these studies do not include sufficient information on the level of exposure to either cadmium or to other metals to permit assessment of this problem.

Increased mortality from NMGID has not been reported previously in association with cadmium. Ingested cadmium is a severe gastrointestinal irritant in man (*5*, *28*), and Tsuji et al. (*29*) and Adams et al. (*30*) have commented on the frequent observation of gastritis and gastrointestinal ulceration among chronically exposed persons. In our study we observed a 2.8-fold overall increase in deaths from NMGID (excluding cirrhosis of the liver) among workers employed on or after January 1, 1926. Deaths from these causes showed a general association with prolonged employment. Because NMGID previously has not been examined systematically, we view this finding as a hypothesis to be examined further in future studies rather than as a definitive conclusion.

No new deaths from prostate cancer have occurred in this cohort since the Lemen study (*1*). In addition, 1 of the 4 original cases was excluded from this analysis because of the revised definition of the cohort. The excluded worker had been employed for 18 years as a guard who patrolled the entire plant but at no time had worked for 6 months in a production area. Exclusion of such a worker is to a certain extent arbitrary. Also, because the small size and short additional follow-up of this cohort has low statistical power, and because prostate cancer is frequently a nonfatal disease imperfectly studied by death certificate data, we believe that the absence of new cases during the 5 additional years of follow-up weakens but does not refute the possible association between cadmium and prostate cancer.

The presence of only 1 death attributed to chronic renal failure is interesting, inasmuch as cadmium is a known nephrotoxin and because increased mortality from chronic nephritis and nephrosis has been noted among Swedish battery workers (*15*, *16*). The difference may well be due to local differences in recording certain types of information on death certificates. The comparisons in our study were based upon the underlying causes of death and ignore the data for 4 individuals for whom renal disease was noted as a contributing cause of death. Impaired renal function frequently is underreported on death certificates, even when the disease was sufficiently severe to require chronic hemodialysis (*41*).

In contrast to the Lemen study (*1*), we found no excess of deaths from nonmalignant respiratory disease either in the overall cohort or among workers with 2 or more years of employment. If deaths from silicosis are excluded, the only increase in mortality from these causes is among workers with short-term employment. The significance of this finding is unclear.

In summary, the finding of increased lung cancer mortality in this follow-up analysis is consistent 1) with the previous mortality study of this cohort (*1*), 2) with the recently published rat inhalation study (*13*), and 3) with the epidemiologic findings of Sorahan and Waterhouse (*18*). An association of cadmium with NMGID was also observed. Previous findings (*1-3*) of prostate cancer among exposed workers were somewhat weakened.

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Metallothionein
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FUNCTIONS OF HEPATIC AND RENAL METALLOTHIONEINS IN THE CONTROL OF THE METABOLISM OF CADMIUM AND CERTAIN OTHER BIVALENT CATIONS

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As the first metallothionein to be isolated (1) contained a high content of Cd^{2+}, it was a logical assumption that one function of thionein might be to provide a defence mechanism against this toxic cation. This possibility, amongst others, was considered by Kägi and Vallee (2,3) and was developed by Piscator (4) as an hypothesis to explain the progressive accumulation of biologically inert Cd^{2+} in the livers and kidneys of rabbits, exposed to repeated small doses of $CdCl_2$. The detoxification function of thionein against low level exposure to either parenterally, or orally, administered Cd^{2+}, was confirmed in a number of later investigations (5-10, see also ref.11). These investigations established clearly that much of the high body burden of Cd^{2+} accumulated by the experimental animal under these conditions was present as the metallothionein in the livers and kidneys, and thus was unavailable for interaction with processes with important biological functions. Other studies suggested that the inducible synthesis of thionein in these organs is not limited to Cd^{2+}, but probably functions under conditions of either chronic exposure to Hg^{2+} (12), or increased tissue concentrations of the essential, but potentially toxic, Zn^{2+} and Cu^{2+} cations (e.g. refs. 13 & 14).

Pretreatment of experimental animals with a low dose of Cd^{2+}, or higher dose of Zn^{2+}, is known to protect them against a subsequent, normally lethal, dose of Cd^{2+} (15) and also to prevent the Cd^{2+}-induced testicular damage (16,17), placental haemorrhage (18) and foetal malformations (19-21). As both pretreatment cations stimulate the synthesis of the corresponding metallothioneins, protection against such acute effects of Cd^{2+} also has been attributed to these metalloproteins (6,8,22-25). Since Zn^{2+} is a common component of the metallothioneins that are induced by both Cd^{2+} and Zn^{2+}, it is possible that such protection could result from the replacement of this cation by Cd^{2+}. Alternatively, pretreatment might eliminate the lag in thionein synthesis (26), such that further production of the protein is an immediate response to subsequent challenge with Cd^{2+}. There is some experimental support for both of these possibilities. Thus Cd^{2+} has been shown to displace Zn^{2+} from zinc-thionein (7,8) and from (cadmium, zinc)-thionein (22,24), in the livers of animals pretreated with Zn^{2+} and Cd^{2+} respectively. Yoshikawa (27) and Suzuki and Yoshikawa (22) consider that this

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replacement of Zn^{2+} in presynthesized (cadmium, zinc)-thionein leads to a more rapid accumulation and immobilization of Cd^{2+} in the liver of the pretreated animal and, as a result of this, uptake of the cation by other organs is decreased. According to Leber and Miya (24) the hepatic concentration of (cadmium, zinc)-thionein in mice, and thus of replaceable Zn^{2+}, increases with the pretreatment dose, as does the tolerance to Cd^{2+} on subsequent exposure. A positive correlation between the hepatic content of this metallothionein and the LD_{50} of Cd^{2+} in mice after pretreatment with different doses of the cation also has been reported by Probst et al. (25). Treatment of rats with an oral dose of Cd^{2+} (20 mg/kg) was found by Squibb et al. (23) to protect against a second (100 mg Cd^{2+}/kg), given after 24h. and to increase the uptake of Cd^{2+} not only in the liver, but also in the kidneys and testes (cf. Yoshikawa (27), Suzuki and Yoshikawa (28)). In non-pretreated (control) animals, hepatic thionein synthesis exhibited the usual lag and thus, during the first few hours after the oral administration of Cd^{2+} (100 mg/kg), most of the cation that was taken up by the liver was associated with the high molecular weight proteins of the cytosol. In the pretreated animals, however, the lag phase was eliminated and, from the earliest times after the administration of the second dose, all of the Cd^{2+} in the soluble fraction of the liver was bound to thionein (23).

Whilst these investigations seem to support the concept of a protective function of pre-induced (cadmium, zinc)-thionein against the acute toxicity of Cd^{2+} there are other observations which are difficult to reeencile with this view. For example, protection can be obtained with, and is effective against, other cations that do not induce thionein synthesis. Thus In^{3+} and Mn^{2+} protect against acute doses of Cd^{2+} (28), and pretreatment with Pb^{2+} confers protection against toxic doses of Pb^{2+} (29). Also, protection against Cd^{2+} in rats has been shown to be maximal 1-3 days after pretreatment with a low dose of Cd^{2+} and then to decrease with time (30). Both the content of the pre-induced metallothionein, as well as the capacity for the immediate synthesis of this metalloprotein, however, were retained in the liver of the pretreated animal for a much longer period. In agreement with the observations of Yoshikawa (27), Suzuki and Yoshikawa (22), Squibb et al. (23), and Cherian and Vostal (31), hepatic uptake of Cd^{2+} was found to be much greater in the pretreated animals than in the non-pretreated controls. Uptake of the cation by the kidney, spleen, pancreas, brain and heart, however, was unaltered, whilst faecal excretion was decreased. The increased retention in the liver, therefore, probably was due to decreased biliary excretion of Cd^{2+} that is known to result from pretreatment (31).

The synthesis of hepatic zinc-thionein is stimulated by restriction of food intake (32), but Webb and Verschoyle (31) have shown that the intravenous LD_{50} of Cd^{2+} in starved rats is the same as that in normally fed animals. Also, even though weanling rats contain very high concentrations of zinc-thionein in their livers, the LD_{50} of intraperitoneally administered Cd^{2+} is not significantly different from that in adult females (G.P. Samarawickrama and M. Webb, unpublished observations).

The above discussion suggests, therefore, that the acute toxicity of Cd^{2+} is not determined by the hepatic concentration of presynthesized zinc-, or (cadmium, zinc)-thionein. Webb and Magos (33) also conclude that the presence of the latter metallothionein in the kidneys of Cd^{2+}-pretreated rats cannot explain the resistance of these animals to normally nephrotoxic doses of Hg^{2+}. In this work, for example, Cd^{2+}-pretreatment was found to increase not only the renal content of thionein-bound-Hg^{2+}, as observed previously by Suzuki (34) and Shaikh *et al.* (35), but also the contents of Hg^{2+} in other cellular components. As, at normally nephrotoxic doses, increased Hg^{2+}-incorporation into these components was greater than that into the metallothionein, it seems that there is no obvious reason to attribute the protective effect of Cd^{2+} to the induction of thionein synthesis, and other mechanisms (cf. e.g. 36) seem more probable.

Whilst, therefore, a role for thionein in the detoxification of certain heavy metal ions seems to be established clearly only at continuous low level exposure, this is unlikely to be the normal physiological function of the protein. It has been suggested that either thionein itself (37), or its copper derivative (38), may be the biologically active molecule with functions in the maintenance of redox potentials (37), ion transport (37), metabolic pools of cysteine residues (39), and in bioenergetic systems, particularly when the contents of cytochrome c oxidase are low (38). There is also much evidence that the primary biological function of this inducible protein is related to the metabolism of the essential Zn^{2+} cation (7,8,32,40-44). According to Chen *et al.* (43,45), zinc-thionein, which accumulates in the livers of rats that are maintained on a diet with high levels of Zn^{2+}, is eliminated within 3 days when the animals are transferred to a Zn^{2+}-deficient diet, the loss being associated with increased urinary and faecal excretion of low molecular weight Zn^{2+} complexes. They conclude, therefore, that thionein has a fundamental role in the accumulation of excess Zn^{2+}, rather than in the storage of the cation for subsequent utilization. A conservation function, however, is indicated by the formation of hepatic zinc-thionein in the rat during post-surgical trauma (46) and in response to starvation (32,44).

Regulation of Zn^{2+} absorption in rats, attributed by Cotzias et al. (47) to negative-feedback control, was shown by Evans et al. (48) to be mediated, at least in part, by the Zn^{2+}-content of the intestinal mucosa which, in turn, is regulated by the Zn^{2+}-concentration of the plasma. Previously a function of thionein in the regulation of the absorption and/or transport of both Zn^{2+} and Cu^{2+} seemed to have been established by the isolation of metalloproteins, tentatively identified as zinc- and copper-thioneins from the intestinal mucosa of the chick (49), rat (50) and bovine (51). Later work by Evans and collaborators (48,52-55), however, established that Zn^{2+}-absorption is determined not by the formation of zinc-thionein, which is absent from the intestinal mucosa of the rat when the rate of absorption is high, but by a low molecular weight peptide (55), that acts as a ligand for Zn^{2+} in the mucosa, and the degree of saturation of the cation-binding sites of the carrier protein, albumin (53,56), or transferrin (57), in serum. This work was confirmed and extended by Richards and Cousins (44,58,59) who produced evidence that absorption of Zn^{2+} in the rat was related directly to the presence in the intestinal mucosa of the Zn^{2+}-chelate of the low molecular weight ligand and inversely to the synthesis of zinc-thionein. These authors suggest that, in cells of both the liver and intestinal mucosa, the contents of this metallothionein are correlated with the serum Zn^{2+}-concentration; in the former, synthesis of zinc-thionein is considered to control uptake and storage of Zn^{2+} and, in the latter, to form an alternative cation-binding species, which acts competitively with the Zn^{2+}-carrier peptide to regulate the transfer of the cation to the blood.

At present, there are difficulties in the application of this regulatory hypothesis to the pregnant animal, in which transfer of Zn^{2+} from the mother to the foetus must be related to the Zn^{2+}-concentration in the maternal blood. As was observed initially by Kägi (60), metallothioneins seem to be present in large amounts in certain foetal tissues. High concentrations of zinc-thionein, for example, occur in the livers of foetal rats (61, G.P. Samarawickrama and M. Webb, unpublished observations) rabbits and human-beings (A. Bakka and M. Webb, unpublished observations), and of (copper,zinc)-thioneins in the livers of murine (A. Bakka and M. Webb, unpublished observations), bovine (62) and probably porcine (63) foetuses. In the liver of the foetal rat, the concentration of thionein-bound-Zn^{2+} may exceed 70 μg/g wet wt. tissue and yet be at or near the limit of detection by conventional methods of analysis in the maternal liver (G.P. Samarawickrama and M. Webb, unpublished observations). Although the variability in cation contents of different foetal metallothioneins might be considered to be indicative of a storage or protective role, there is some

evidence to suggest that hepatic zinc-thionein of the rat foetus, at least, may be of functional significance (A. Bakka, G.P. Samarawickrama and M. Webb, unpublished observations). Thus, in these foetal livers, the content of thionein-bound-Zn^{2+} increases rapidly from the 16th day of gestation and, at birth, may be between 70 and 100 μg/g wet wt. tissue. After birth, the hepatic concentration of the metallothionein at first increases, but at a slower rate, to a maximum at about 7 days. It then falls almost to zero at 18 days. Intravenous administration of Cd^{2+} (1.25 mg/kg) to the pregnant rat on the 16th day of gestation prevents subsequent accumulation of zinc-thionein in the foetal livers. This seems to be due to the inhibition of Zn^{2+}-transport by Cd^{2+} in the maternal placenta, and not to the small amount of the latter cation that enters the foetus at this dose level, and which is bound by the metallo-thionein of the foetal liver. Inhibition of Zn^{2+}-transport persists for the remainder of gestation, although it decreases slowly (e.g. from 84% at 4h. after Cd^{2+}-administration to 66% at 48h.) with time.

If accumulation of zinc-thionein provides a defence mechanism against excess Zn^{2+} during normal foetal development, the content of the metalloprotein might be expected to remain low in the livers of the newborn pups of the Cd^{2+}-treated mothers. In these litters, however, the hepatic concentration of zinc-thionein increases to reach approximately the same maximum (60–80 μg thionein-bound-Zn^{2+}/g wet wt. tissue) at the same time as that in normal newborn animals. Fractionation of the liver cytosol of the weanling animal shows that, once the content of hepatic zinc-thionein reaches its maximum and begins to decrease, the contents of both Zn^{2+} and protein in one of the high molecular weight fractions increase. The gain in Zn^{2+} by this heterogeneous fraction which, as shown originally by Bremner and Marshall (64) and Bremner and Davies (46), contains super-oxide dismutase and carbonic anhydrase, is not stoichiometric with the loss from the metallothionein; an observation that possibly is to be expected from the findings of Chen *et al.* (43,45) on the elimination of thionein-bound-Zn^{2+} from the liver of the Zn^{2+}-loaded adult rat. These results, therefore, indicate but, at present, provide no firm evidence to support, the possi-bility that accumulation of hepatic zinc-thionein during late foetal and early post-natal life in the rat may be related to subsequent requirements for the cation in the synthesis of other metalloproteins at later stages of development. Such a function has been considered previously for neonatal mitochondrocuprein (65), which is regarded as a polymeric form of partially loaded copper-thionein (65,66), and may act as a reservoir of Cu^{2+} for the subsequent formation of cytochrome-c oxidase, the content of which increases rapidly during the neonatal period.

It is possible that, if copper-thionein undergoes polymerization *in vivo* to mitochondrocuprein, the presence of zinc-thionein in some foetal livers, and of (copper, zinc)-thionein in others, may be correlated with the content of this insoluble copper-protein. This would imply that copper- and zinc-thioneins occur as separate species, and thus would be contrary to current concepts that both cations are present, though in different ratios, in all forms of (copper, zinc)-thioneins (67,68). Whilst this may be true when the Cu:Zn ratio is high, it has been shown that crude preparations of (copper, zinc)-thionein (atomic ratio Cu:Zn = 1:1) from 1-8 day old pig liver, yield zinc-thionein as a single molecular species on preparative electrophoresis (63). No evidence has been obtained, however, that the hepatic content of mitochondrocuprein in newborn pigs is related to the tissue content of Zn^{2+} (63). Such a relationship might be expected if Zn^{2+} either prevents the polymerization of copper-thionein to mitochondrocuprein, or plays a role in the metabolism and elimination of this insoluble protein from the liver of the newborn.

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Validation Attempts of a Generic Approach for Regulating Air Toxics

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The validity of deriving ambient air quality standards or levels via threshold level values (TLVs) is assessed via two methodologies: (1) using current U. S. standards for ambient air standards and occupational standards where the data base is very robust and (2) using Soviet occupational and community air standards where the standards are based on experimentally derived toxicological endpoints. The analysis indicates that the TLV-derived approach using TLV/420 and the appropriate averaging time is in wide disagreement with both validating methodologies. © 1986 Academic Press, Inc.

INTRODUCTION

Many states have initiated an attempt to develop "air toxics" regulations in the absence of a nationwide program on the federal level. Given the recognition that low concentrations of dozens of agents exist in ambient air, many states are opting for generic approaches to deriving acceptable air quality levels. While there are a number of variations, the basic pattern is often the same. This embodies the delineation of an ambient air quality standard (AAL) via a conversion of the industrial threshold level values (TLV) as derived by the American Conference of Governmental Industrial Hygienists (ACGIH). Since the TLV is based on predicting the health of occupationally exposed persons it usually assumes that exposures are confined to a 40-hr work week (i.e., 8 hr per day, 5 days per week) over the Years 18 through 65. Since ambient exposures entail 168 hr exposure each week (i.e., 24 hr per day, 7 days per week) over an entire lifetime (i.e., conception to death), various proposed modifications of the TLV have been proposed in order to make it more relevant to the ambient condition.

That an occupational health standard should be applied for deriving ambient air standards is highly controversial and not uniformly accepted. Nevertheless, it appears that many state regulatory offices have adopted what is widely considered a "pragmatic" approach. Since over 500 TLVs exist and have gone through a form of peer-review process and since the cost of doing each agent separately would be enormous, they have opted for some type of generic TLV-derived ambient standard regardless of the toxicological "correctness" of using TLVs for this purpose.

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In practical terms what frequently occurs is that the proposed ambient standard is some fraction of the TLV. For example, it is common for TLVs to be divided by 42 or 420 (TLV/42 or TLV/420), based on dividing the 40 hr per week exposure by 168, which yields 1/4.2, and then applying either a 10 or 100 safety factor. Other modifications may exist if one also wanted to amortize life span versus working years or respiration rate of children versus adults. The present paper is designed to offer two independent attempts to evaluate the validity of the generic approach using a TLV conversion factor for deriving AALs.

METHODOLOGY 1

The first attempt in considering whether dividing TLVs by 420 or some other value is valid is to assess what would be the ratio for agents where there is an enormous reservoir of toxicological and/or epidemiological data existing for both occupational and environmental (i.e., community) exposures. Take for example, SO_2, O_3, NO_2, CO, and Pb for which the United States has both national occupational and ambient air quality standards. If one were to use the TLV of each of these agents and divide by 420, how close would the value come to the ambient standard after adjusting for average periods? Would it underpredict or overpredict the value and by how much? As can be seen in Table 1, the methodology of dividing the TLV by 420 now is consistently more conservative or protective than that derived from actual data. For example, the ambient SO_2 standard for a 24-hr average of 365 mg/m^3 is about 1/13.6 of the occupational standard and not 1/420th of the value! Then, if one employs the current "known" pollutants to validate the proposed methodology, it would show that the TLV/420 approach is consistently more protective than current standards for which large data bases exist.

TABLE 1

COMPARISON OF TLVS AND AMBIENT AIR QUALITY STANDARDS IN THE UNITED STATES

	TLV	Ambient standard	Ambient TLV ratio
CO	50 ppm (~55 mg/m^3)	10 mg/m^3 (8-hr max)	$\frac{1}{5.5}^a / \frac{1}{14.2}^b$
O_3	0.1 ppm (~0.2 mg/m^3)	0.12 ppm (1-hr max)	$\frac{1}{2}^c$
SO_2	2 ppm (~5 mg/m^3)	365 μg/m^3 (24 hr)	$\frac{1}{13.6}$
NO_2	3 ppm (~5 mg/m^3)	0.100 mg/m^3 (annual)	$\frac{2}{5}^d / \frac{1}{60}^e$
Pb	0.15 mg/m^3	1.5 μg/m^3 (monthly)	$\frac{1}{50}^e / \frac{1}{100}^f$

Note. This table is an attempt to compare the U. S. ambient standards with the TLV counterpart.

[a] This represents a comparison of the 8-hr max with the TLV.

[b] This represents a comparison of a calculated 24-hr ave via the CRSTER model with the TLV.

[c] Stokinger (1972) estimate.

[d] This represents a comparison of a calculated 24-hr ave via the CRSTER model with the TLV.

[e] This represents a comparison of the annualized ambient standard with the TLV.

[f] This represents a comparison of the monthly ambient standard with the TLV.

METHODOLOGY 2

Another way to try to judge the validity of the proposed TLV-derived AAL methodology is to consider the relationship of the AAL to the TLV equivalent standard in countries where a large number of both standards are available and where the data are based on toxicologically derived endpoints for both types of standards and not on a TLV-derived methodology. The country with the most available standards for comparison is the Soviet Union.

The Soviet approach to setting acceptable exposure limits for occupational and ambient air pollutants has been written about in some depth in U. S. toxicological journals by both Soviet and American scientists [see Calabrese (1978) for a review]. The approaches used for standard setting by both countries are generally similar when it comes to viewing the AAL in relationship to TLV [or maximum acceptable concentration (MAC) as the Soviets call them]. Both countries recognize that the workplace

TABLE 2

CASES WHERE THE AMBIENT STANDARD IN THE SOVIET UNION IS GREATER THAN 1/420th OF THE OCCUPATIONAL HEALTH STANDARD

	Fraction of the occupational health standard
1. Epichlorohydrin	1/5.0
2. CCl_4	1/9.75
3. Sulfuric acid	1/10.00
4. Phthalic anhydride	1/10.00
5. Lead	1/14.2
6. Carbon monoxide	1/18.7
7. Benzene	1/22.5
8. Manganese	1/30
9. Hydrogen cyanide	1/33
10. Chlorine	1/33
11. Mercury, metallic	1/33.3
12. Ethylene oxide	1/36.0
13. NO_2	1/42
14. Trichloroethylene	1/48.1
15. HCl	1/49.0
16. Acetone	1/54
17. Pyridine	1/56.2
18. Acrolein	1/60
19. Hydrogen fluoride	1/80
20. Toluene	1/81.2
21. Acetic acid	1/83
22. Formaldehyde	1/100
23. Arsenic	1/100
24. Methyl alcohol	1/104
25. Ammonia	1/108
26. SO_2	1/156
27. Furfural	1/200
28. Ethanol	1/201
29. Xylene	1/261
30. Nitrobenzene	1/375

TABLE 3

CASES WHERE THE AMBIENT STANDARD IN THE SOVIET UNION IS LESS THAN 1/420th OF THE OCCUPATIONAL HEALTH STANDARD

	Fraction of the occupational health standard
31. Phenol	1/494
32. Chlorobenzene	1/506
33. Tetrahydrofuran	1/516.2
34. Propyl alcohol	1/666
35. Aniline	1/1,013
36. Amyl acetate	1/1,050
37. Hydrogen sulfide	1/1,313
38. Methyl acetate	1/1,534
39. CS_2	1/1,800
40. Ethyl acetate	1/1,925
41. Butyl acetate	1/2,130
42. Naphthalene	1/6,666
43. Styrene	1/16,800

standard is designed to protect a worker from an 8-hr exposure for 5 days per week for 50 weeks per year between the normal work years of 18 to 65 years of age. However, an AAL must protect the general public including the young and aged, persons at enhanced risk due to preexisting diseases such as respiratory illness, and others. Consequently, the AAL will be a much lower number than the TLV (or MAC). The principal difference between the two countries relates to what is termed an "adverse health effect." The Soviets consider any physiological/biochemical deviation from normal as unacceptable. However, the United States may view certain initial alterations (e.g., enzyme induction) as indications of an adaptive response. The net result is that Soviet standards for both MACs and AALs are often considerably lower than their U. S. counterpart standards (Izmerov, 1973).[1]

Regardless of these differences, the ratio of AAL to TLV should be comparable between the two countries. This is one reason why it is deemed of great interest to see to what extent the Soviet AAL is a mathematical relationship of their MAC. In addition, the Soviet AALs are actually based on experimental studies usually with animal models focusing on the most sensitive biological parameters such as olfactory response, enzyme alterations, etc., along with 0.3-fold safety factor down from the no effect level.

In the present evaluation, 114 Soviet AALs were obtained. From this total, forty-three 24-hour average AALs with corresponding MACs [i.e., 8-hr maximum (not time weighted)] values (Tables 2 and 3) were compared. The remaining 71 AALs were not compared because of a lack of available MAC, no 24-hr average value, etc. The results indicated that about 70% (30 of 43) of the AALs had values that were considerably higher than the 1/420 TLV methodology. Thirteen of the 43 agents had values much lower than the 1/420 TLV proposed methodology. The total variation was enormous, being from 1/5 to 1/16,800 of the MAC! The toxicological basis for such differences is known from the U. S. literature for but a few of these agents. Nevertheless, it is known that these values are experimentally derived and not just a numerically con-

[1] It should be noted that we are not discussing compliance with the proposed standards.

jectured value. This being the case, it calls into question the generic approach which treats all agents in a similar manner. If the Soviet approach were a good model, it would suggest that the TLV/420 methodology would often have much "unneeded" safety built in, while at other times not enough.

DISCUSSION

The two independent attempts to validate a currently in vogue methodology for deriving AALs from TLVs indicate potentially serious problems. The U. S. data, based on our current ambient air standards, suggest that the TLV/420 methodology may grossly overpredict risk while the Soviet data imply that this methodology may grossly under and/or overpredict risk based on the agent. While any generic approach would be expected to be somewhat off the mark and on the conservative side, the magnitude of the potential inconsistencies is so large as to seriously question the validity of this approach. Clearly, further attempts to assess the validity of this and other generic approaches to establishing public health-based AALs are needed before such standards become adopted in numerous states.

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ISOLATED/
SED LIVER.
rles H. Hobbs

)CHLORIDE.

BESTOS EX-
Joan O. Ford

VBORN RAT.

MEMBRANES

atory/Analgesic

INFLUENCE OF TOTAL DOSE AND DOSE RATE IN CARCINOGENICITY STUDIES

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One element of the ED_{01} Study contained a group of animals that were dosed with 2-acetylaminofluorene for 9, 12, 15, 18, or 24 mo and then sacrificed at 18 or 24 mo. This provided data to compare the relative effects on carcinogenicity of dose rate versus total dose. The prevalence of liver and bladder tumors were used as the comparison. Animals receiving similar total doses but over a different length of time (different dose rates) were compared at the 18- and 24-mo sacrifices. When the total doses were similar, the higher dose rates for shorter time periods induced a higher prevalence of tumors. Results were more consistent for bladder tumors than for liver tumors, although the same trends were noted for both endpoints. Those groups dosed at higher rates but for fewer months had a generally higher prevalence than those receiving similar total doses but at lower rates for more months. This data from the ED_{01} Study illustrates the importance of experimental design, dosing regime, length of study time, and age of the animals at time of dosing in respect of calculation of risk.

INTRODUCTION

Chronic toxicology studies for the determination of carcinogenicity are usually conducted by administering the agent to the animals in their feed or water at calculated concentrations for specified lengths of time. These studies often include sacrifice intervals in which part of the animals are removed from the study and an examination made at some interim point in the lifetimes of the animals. These studies are generally terminated around the average lifespan of the animal species on study. At the terminal sacrifice, the animals are killed and microscopic histopathological examinations conducted. Estimates of risk are calculated on positive studies based on the concentration of the test agent in the feed or water of the test animal. Almost always, studies are conducted in which dosages are administered ad libitum and continue until the time when the animal is removed from the study. One element of the ED_{01} Study (Littlefield et al., 1980), a study performed to determine the possibility of determination of the effective dose of a carcinogen at the 1% level, contains groups of animals that were dosed for specific periods of time, after which the carcinogen was removed

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removed from the feed and the animal was subsequently held for additional time periods prior to sacrificing. Since concentrations of the carcinogen were determined analytically in each batch of feed and feed consumption was measured, the data are available to study the effects of dose rate, or the dose schedule, using several different groups of animals having different dosing periods, but were sacrificed after the same lifespan. The purpose of this paper is to examine the influence that the dosing regime (i.e., dose rate and total dose) may have on the relative results of a carcinogenicity study.

METHODS

The complete methods, results, and analysis of this study are found in Littlefield et al. (1980). The experimental design with respect to numbers of animals sacrificed at each dose level is shown in Table 1. For the purposes of this paper, serial treatment groups are used. BALB/c female mice were dosed at 0, 60, 75, 100, and 150 ppm, in the feed, commencing as weanlings, for 9, 12, 15, 18, or 24 mo, then sacrificed at either 18 or 24 mo. The carcinogen in the feed was 2-acetylaminofluorene (2-AAF). The average total dose in milligrams 2-AAF per mouse was determined using each group of mice that was sacrificed and was calculated from the food consumption data recorded on each cage weekly. The total dose used in the results was based on the average dose per mouse per cage, since some animals in each group died prior to sacrifice. The target concentration was used in the calculation and the total dose was calculated by multiplying the concentration in ppm by the food consumption. The NCTR mouse feeder (Hunziker, 1975) was used. This feeder has been shown to prevent spillage at a rate consistently less than 1%.

Models for estimating liver and bladder tumor prevalence rates are, respectively,

TABLE 1. Number of Animals Sacrificed at Each Dose and Time Interval

	Time of sacrifice (mo)							
	18	24	18	24	18	24	18	24
	Time on dose (mo)							
Dose (ppm)	9	9	12	12	15	15	18	24
150	63	33	63	29	63	28	121	130
100	64	35	65	33	64	35	131	160
75	128	66	132	74	130	86	267	311
60	184	108	190	118	196	114	269	415
0							400	384

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$$\ln(P_L + 0.5) = 2.1236 + 0.004175r + 0.00330d$$
$$P_L = -0.5 + \exp(2.1236 + 0.004175r + 0.003330d)$$
$$\ln(P_B + 0.5) = -1.8428 + 0.00014331r^2 + 0.011020d$$
$$P_B = -0.5 + \exp(-1.8428 + 0.00014331r^2 + 0.011020d)$$

where P_L is the estimated percent of animals with liver tumors (prevalence) at 24 mo, P_B is the estimated percent of animals with bladder tumors (prevalence) at 24 mo, dose rate r is given as ppm 2-AAF, and total dose d is the average milligrams per mouse of 2-AAF. The constants in the exponents of the models were obtained by the method of least squares.

RESULTS

The average total dose received by the respective dose groups of animals and the prevalence of liver and bladder tumors are shown in Table 2.

There are several comparisons that can be made from Table 2, in which animals received a similar total dose but at different dose rates. For instance, mice that received 160 mg 2-AAF at 75 ppm over 24 mo can be compared to another group that received 153 mg 2-AAF at 150 ppm for 12 mo. Both groups were sacrificed at 24 mo. The prevalence of both liver and bladder tumors were higher in the group receiving the higher dose rate for 12 mo. Mice dosed at 60 ppm (128 mg 2-AAF) for 24 mo had the same liver tumor prevalence but a slightly lower bladder tumor prevalence than a group dosed at 100 ppm (133 mg 2-AAF) for 12 mo. Two other groups (97 mg 2-AAF over 15 mo at 75 ppm versus 100 mg 2-AAF over 12 mo at 100 ppm) showed essentially the same results. However, 2 other groupings (78, 77, and 76 mg 2-AAF over a dosing period of 15, 12, and 9 mo at 60, 75, and 100 ppm, respectively, and 61 and 57 mg 2-AAF over 12 and 9 mo at 60 and 75 ppm, respectively) showed somewhat inconsistent results in the liver tumors, while no bladder tumors appeared in these groups. All of the groups already mentioned were sacrificed at 24 mo.

Comparisons that were made in the animals sacrificed at 18 mo showed a lower prevalence in the liver tumors, since this lesion was a late-developing tumor. However, the results in bladder tumors showed some consistent trends. The most prominent example was the two groups having a total dose of 148 mg 2-AAF (100 ppm for 18 mo) and 149 mg 2-AAF (150 ppm for 12 mo). The prevalence was 4% in the group having the 100 ppm dose rate, and 22% in the group having a dose rate of 150 ppm. Two other groups (113 and 114 mg 2-AAF for 18 and 9 mo at 75 and 150 ppm) exhibited a prevalence of 1 and 6%, respectively, while 3 other groups (74, 75, and 71 mg 2-AAF over a dosing period of 15, 12, and 9 mo at 60, 75, and 100 ppm, respectively) showed bladder tumors appearing only in the group dosed at 100 ppm, which was the highest dose rate. This was also noted in groups receiving 91, 94, and 97 mg 2-AAF, and another grouping receiving 60 and

18	24
121	130
131	160
267	311
269	415
400	384

TABLE 2. Total Dose (mg 2-AAF/Mouse) and Subsequent Prevalence of Liver Tumor and Bladder Tumor for BALB/c Mice

		Month of sacrifice							
		18	24	18	24	18	24	18	24
		Months dosed							
Dose (ppm)	Parameter	9	9	12	12	15	15	18	24
150	Total dose	114	116	149	153	186	195	224	316
	Liver tumor, %	6	27	3	31	6	21	6	43
	Bladder tumor, %	6	18	22	24	34	39	51	77
100	Total dose	71	76	97	100	127	133	148	211
	Liver tumor, %	2	14	0	15	2	17	5	30
	Bladder tumor, %	2	0	2	3	0	3	4	16
75	Total dose	56	57	75	77	94	97	113	160
	Liver tumor, %	2	15	5	19	4	16	2	20
	Bladder tumor, %	2	0	0	0	0	0	1	1
60	Total dose	45	45	60	61	74	78	91	128
	Liver tumor, %	1	12	1	9	2	13	3	17
	Bladder tumor, %	0	1	0	0	0	0	1	1

56 mg of 2-AAF; i.e., the higher prevalence was noted in these groups in which the higher dose rate was given over a shorter time period.

The general concensus of these comparisons shows the liver tumor data as not consistent over all ranges, but does exhibit a trend toward a higher prevalence associated with the higher dose rates. The bladder tumor data were more consistent in this respect. When the total doses were similar, the higher dose rates for shorter time periods induced a higher prevalence of bladder tumors.

The total dose was calculated for each treatment group. The respec-

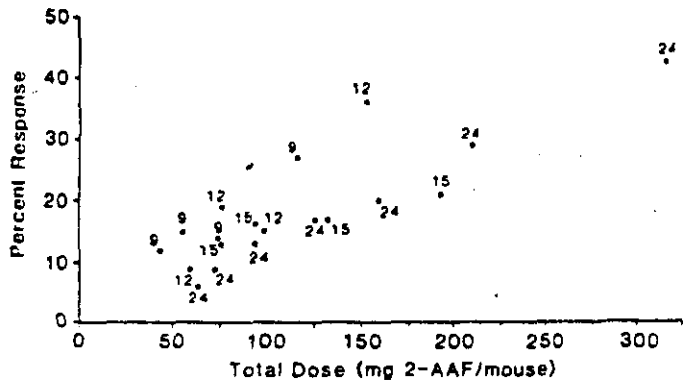

FIGURE 1. Relationship of total dose, dose rate, and incidence of hepatocellular carcinoma in 24-mo-old mice. Number indicates duration of dose (months).

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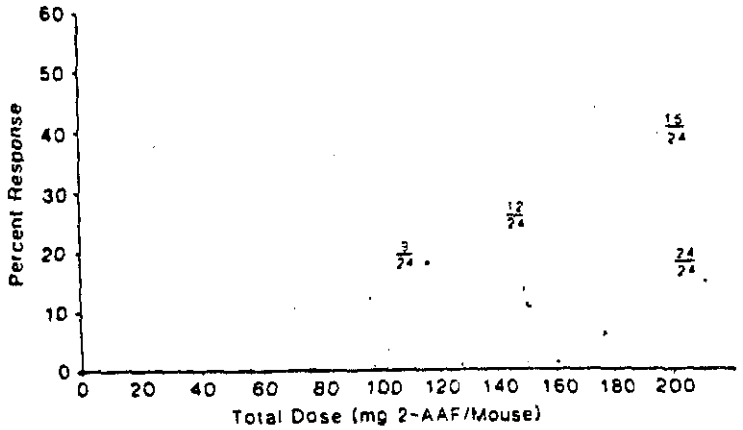

FIGURE 2. Relation of total dose, dose rate, and incidence of bladder tumors in mice sacrificed at 24 mo. Number indicates (months dosed)/(months at sacrifice).

tive prevalence of hepatocellular carcinoma for each of these treatment groups was determined and the resulting data are shown in Fig. 1. The total dose (mg 2-AAF/mouse) is compared against the prevalence at the 24-mo sacrifice. Those groups dosed at higher rates, but for fewer months, have a generally higher prevalence than those receiving similar total doses, but at lower rates for more months. Therefore, the dose rate appears to influence the prevalence of hepatocellular carcinomas irrespective of the total dose. For example, mice receiving a total dose of 153 mg 2-AAF over a period of 12 mo had a prevalence of 31% hepatocellular carcinomas, as compared to only 20% in mice receiving a total dose of 160 mg 2-AAF over a 24-mo period.

For bladder tumors, the same effect is noted in Fig. 2. A dose-rate effect is very evident, in that the animals receiving the same dose but over a shorter time interval had the higher prevalence of bladder tumors.

DISCUSSION

The data presented indicate that under the conditions of this study, both dose rate and length of exposure (total dose) influence the carcinogenic response. Animals dosed for 9 or 12 mo and sacrificed at 24 mo had a much higher prevalence of both liver and bladder tumors than a group given a similar total dose for 18 or 24 mo. This has important implications related to choices of experimental designs, especially in quantitative carcinogenesis studies designed for calculation of risk. For instance, 160 mg 2-AAF administered over 24 mo resulted in a 20% prevalence of liver tumors, whereas approximately the same total dose of 153 mg given for 12 mo (i.e., at twice the dose rate), with the sacrifice at 24 mo, resulted in a prevalence of 31% liver tumors, a 55% increase in tumor prevalence. Higher dose rates for shorter periods of time appear to be more effective for producing positive

results than lower dose rates given over longer periods of time. This also supports the concept that smaller numbers of animals at higher dose rates could be used to obtain significant results. Also, in view of the high cost of conducting toxicology studies, costs could be reduced by dosing the animals for the first 9 to 12 mo, then merely holding them until sacrifice at 24 mo. This would eliminate the cost of diet preparation and subsequent chemical analysis and diet monitoring for 12-15 mo. However, this reduces the chance of detecting tumors compared to using the higher dose rate for 24 mo. Also, dose rates are limited to the amount that animals can tolerate.

The amount of data in the literature in which total dose can be compared with dose rate is sparse. One study, conducted by McCornick et al. (1981), gave a total dose by intragastric instillation of 30, 20, or 15 mg *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine in 20, 10, or 5 weekly fractions. These data showed that the doses given in the 20 weekly fractions were more effective in producing urinary bladder cancer than those given in the 5 weekly fractions. Although it is not clear whether the 5 weekly fractions were given in the first 5 wk or evenly spread throughout the 6-mo study period, these higher dose rates did not produce the same results as the present study. Although the reason is not clear, it could be due to a chance for recovery with the five fractions.

Druckrey (1967) stated that the total dose needed to produce cancer with small daily doses over a long period is not greater, but significantly smaller. Carcinogenic action goes considerably beyond a pure "summation action" and increases with time. Druckrey theorized that time is inversely proportional to dose. Druckrey showed that the tumor rate decreases when the total dose of diethylnitrosamine is spread at lower doses over a longer time. In the study reported here, all animals were sacrificed at the same time, therefore, time is not a factor.

Another factor that possibly had an influence in this study is that in many instances young animals are more susceptible to exposures of carcinogens than older animals. Therefore, since the higher dose rates were administered to the animals during the first 9 or 12 mo of their lifespan, they might exhibit the higher prevalences.

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The inhalative toxicity of different cadmium compounds in rats*

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Abstract. In a long-term inhalation study, male and female Wistar rats were continuously exposed to submicron aerosols of CdO, $CdCl_2$, $CdSO_4$, CdS and a CdO/ZnO combination. For chronic exposures it was shown that at aerosol levels equal to and above 90 µg/m³ Cd, even the less soluble cadmium compounds (CdO and CdS) were toxic and lethal, especially to male rats. No mortality was seen in the group exposed to the ZnO/CdO combination. Our study suggests that inhalative toxicity of cadmium compounds may be related to lung retention of bioavailable cadmium. In a short-term inhalation study we found that the lung retention of cadmium was two times higher after exposure to CdO than to $CdCl_2$. The lung and body burden of cadmium differed by a factor of ten between CdO and CdS. The reasons behind these results are not yet fully understood.

Key words: cadmium compounds - inhalation - retention - toxicity - Wistar rats

Introduction

It has been shown from long-term inhalation studies that cadmium chloride induced primary lung tumors in Wistar rats, and that the incidence of lung tumor was strongly dependent on the cadmium aerosol concentration [Takenaka et al. 1983, Oldiges et al. 1983, Oldiges et al. 1984]. It was therefore logical to examine whether other less soluble cadmium compounds to which human beings are more frequently exposed have the same carcinogenic potency as cadmium chloride.

Material and methods

Long-term inhalation study

In a long-term inhalation study rats were exposed to cadmium aerosols consisting of cadmium chloride ($CdCl_2$), cadmium oxide (CdO) as dusts and fumes, cadmium sulfate ($CdSO_4$), and cadmium sulfide (CdS). Another group of rats was exposed simultaneously to dusts consisting of zinc oxide (ZnO) and cadmium oxide. The rats were exposed in 225 l horizontal flow inhalation chambers. Two wire mesh cages were placed in each chamber and each cage contained 10 rats.

The aerosols were generated by several different systems described previously [Hochrainer 1983]. The aerosol flow-rate was 80 l/min. The particles of the cadmium aerosols were in the submicron size range and had average mass medium diameters ranging from 0.2 to 0.5 µm. The particle size distributions and the cadmium aerosol concentrations were measured as described elsewhere [Oberdörster et al. 1979].

Five week-old inbred Wistar rats (TNO-W-75, SPF) were used. For each aerosol concentration and for each cadmium compound there were 20 female and 20 male rats, purchased from F. Winkelmann GmbH, Borken, FRG. 40 animals breathing filtered air were kept as controls (Table 1). The inhalation laboratory is an air-conditioned room with a 12 hrs day/night cycle. The animals received drinking water ad libitum. To keep the cadmium uptake from food as low as possible the animals were fed with a Ssniff pellet diet between 4 p. m. and 8 a. m. The rats were continuously exposed for 22 hrs a day, 7 days a week. As in the previously reported experiment the exposure time was to be 18 months and the studies were to be terminated in the 31st month, that being the mean survival lifespan of the strain.

Short-term inhalation study

To obtain more information about the lung deposition and retention of the different cadmium compounds, short-term inhalation studies with 100 µg/m³ Cd as cadmium chloride, 100 µg/m³ Cd as cadmium oxide dust and 1 mg/m³ Cd as cadmium sulfide were performed.

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Correspondence to Dr. Oldiges.

Table 1 Inhalative toxicity of different cadmium compounds in rats

Group No		nominal aerosol concentration (µg/metal/m³)	measured concentration (µg/metal/m³)	duration of the study (days)	exposure (days)	mortality incidence
1.)	controls	♂♂ -	-	343	-	1/20
2.)	controls	♀♀ -	-	343	-	0/20
3.)	$CdCl_2$	♂♂ 30	29 ± 5	255	255	0/20
4.)	$CdCl_2$	♀♀ 30	29 ± 4	255	255	0/20
5.)	$CdCl_2$	♂♂ 90	91 ± 14	441	180[a]	0/20
6.)	$CdCl_2$	♀♀ 90	92 ± 13	441	180[a]	1/20
7.)	CdO dust	♂♂ 30	30 ± 4	343	343	0/20
8.)	CdO dust	♀♀ 30	26 ± 4	343	343	0/20
9.)	CdO dust	♂♂ 90	90 ± 9	343	218[b]	6/20
10.)	CdO dust	♀♀ 90	81 ± 8	343	324[b]	6/20
11.)	CdO/ZnO dusts	♂♂ 90/900	102 ± 20/945 ± 106	374	374	0/20
12.)	CdO/ZnO dusts	♀♀ 90/900	103 ± 20/949 ± 136	374	374	0/20
13.)	$CdSO_4$	♂♂ 90	95 ± 14	455	413[b]	6/20
14.)	$CdSO_4$	♀♀ 90	92 ± 13	455	455	1/20
15.)	CdS	♂♂ 90	91 ± 17	409	409	1/20
16.)	CdS	♀♀ 90	92 ± 20	402	402	0/20
17.)	CdS	♂♂ 270	254 ± 78	409	409	3/20
18.)	CdS	♀♀ 270	263 ± 75	409	409	2/20
19.)	CdS	♂♂ 810	843 ± 211	409	208	6/20
20.)	CdS	♀♀ 810	841 ± 209	402	298[b]	7/20
21.)	CdS	♂♂ 2430	2270 ± 545	112	112[b]	5/24
22.)	CdS	♀♀ 2430	2247 ± 543	105	105[b]	4/24
23.)	CdO-fume (n = 40)	♂♂ 10	10 ± 3	243	243	0/40
24.)	CdO-fume (n = 40)	♂♂ 30	31 ± 4	243	249	0/40

a) The planned inhalation time was 180 days

b) exposure interrupted due to more than 25% mortality

A higher concentration of cadmium sulfide was chosen because of the very low solubitiy of this compound. Groups of six five-week-old male rats were continously exposed to the cadmium aerosols for one month under the same conditions as described above. After exposure each parallel group breathed filtered air for a further two month period before being sacrificed (using urethane anesthesia).

Results

Long-term inhalation study

Since there were no results in the literature regarding the long-term inhalative toxicity of cadmium compounds other than our own with cadmium chloride, we chose higher cadmium aerosol concentration for cadmium sulfate, oxide and sulfide, because of their lower solubilities. However, in some cases the chosen aerosol concentrations were too toxic and those exposures were stopped. For these groups mortality occurred within a few weeks, suggesting that there is a critical lethal concentration. This toxicity (Table 1) was not apparent earlier, either through the regular checks on weight gain, food and water consumption, or by hematological examinations. Gross necropsy of the dead animals revealed increased lung weights and enlarged thoracal lymph-nodes. Elevated liver weights were found only in the rats exposed to the highest cadmium sulfide aerosol concentration (2.4 mg/m³ Cd) (Table 1). No further mortality occurred after termination of cadmium exposure in those groups which had shown increased mortality incidence. The weight gains of the surviving rats were similar to those of the controls. The selected cadmium aerosol concentrations of the different cadmium compounds and the available results (Table 1) show that at 90 µg/m³ Cd or higher, cadmium was toxic as an oxide, a sulfate or a sulfide, especially to the male rats. There was no lethality observed in the cadmium zinc combination group. Cadmium sulfide proved to be toxic with a clear-cut aerosol concentration dependency.

In an earlier experiment we showed that cadmium chloride aerosols had a lung clearance half-life of about 60 days (Oberdörster et al. 1980). The results of this study showed that this must be true for cadmium oxide and sul-

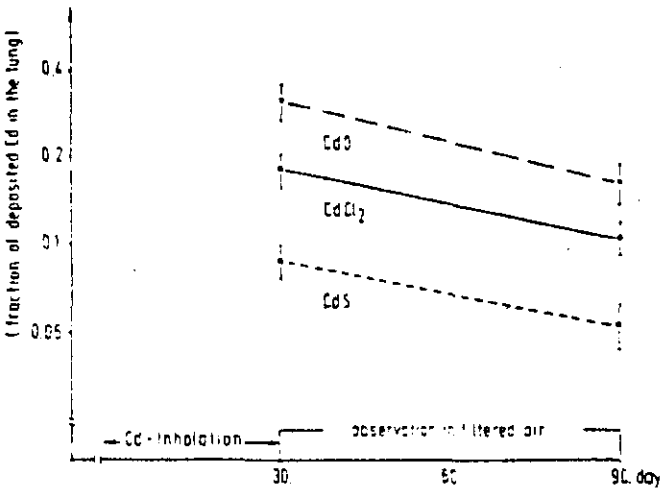

Fig. 1. Cadmium retention in the lung of male Wistar rats (n = 6 per group) after continuous exposure to submicron cadmium aerosols (0.1 mg · m^3 Cd as $CdCl_2$ and CdO, 1 mg/m^3 Cd as CdS). Numbers on ordinate represent relative lung burden, calculated from Stahl's formula with a 30% deposition rate in the alveolar region.

fide aerosols as well (Figure 1). This figure shows that continuous exposure to submicron cadmium aerosol as CdO resulted in a cadmium retention in the rats' lungs two times higher than for treatment with a cadmium chloride aerosol of the same concentration and particle size. Exposure to the less soluble CdS aerosol also resulted in a lower Cd retention in the lungs. In addition to the results for cadmium retention in the lungs, Figure 2 gives the cadmium distribution found in the kidneys and livers. It is evident that cadmium exposure as cadmium sulfide, although ten

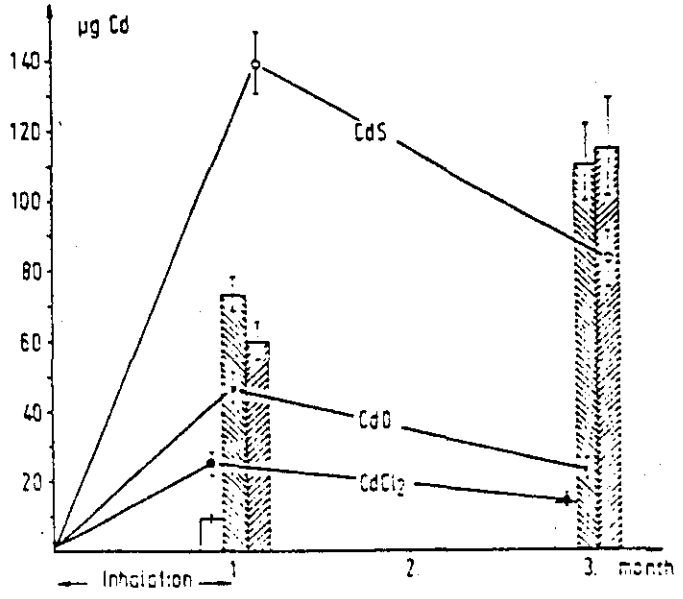

Fig. 2. Cadmium retention in the lungs (line) and Cd body burden in the kidneys and livers (column 1: 0.1 mg · m^3 Cd as $CdCl_2$, column 2: 0.1 mg · m^3 Cd as CdO, column 3: 1 mg · m^3 Cd as CdS) after a one month inhalation and a subsequent two month observation period. Means ± S.D. of 6 male rats each group.

times higher, resulted in the same cadmium body burden as for the exposure to the CdO aerosol. This was observed at the end of the 30-day inhalation period and at the end of the subsequent observation period. These results support the available results of the long-term inhalation study that in addition to the soluble cadmium chloride aerosols, the submicron Cd-aerosols of lower solubilities are just as bioavailable and just as toxic to experimental animals.

Discussion

Several authors suggested that in some occupations cadmium aerosols may be a carcinogenic risk [Lemen et al. 1976, Kjellstrom et al. 1979]. Recently it was demonstrated that long-term exposure of experimental rats to submicron aerosols of cadmium chloride induced primary lung tumors at even low exposure level [Takenaka et al. 1983]. But presently there is no clear knowledge about the kinetics and inhalative potencies of other cadmium compounds, especially the less soluble ones. Thus a long-term inhalation study was designed to describe the carcinognic risk from CdO dusts and fumes, $CdSO_4$, CdS and a CdO/ZnO combination. But in relation to $CdSO_4$ as well as the water insoluble compounds CdO and CdS, it was shown that aerosol levels equal to or higher than 90 µg/m^3 were toxic and lethal to male Wistar rats. Epidemiological data of Princi [1947] and Teculescu and Stanescu [1970] did not reveal any symptoms of toxcicity after inhalation of CdO and CdS dusts and fumes at even higher exposure levels. Our findings concerning toxcicity of these Cd compounds have been confirmed by short-term kinetic studies. Hadly et al. [1980] found that CdO instilled intratracheally rapidly translocated to the livers of rats. The results of Cd retention in this study confirm that CdO was slightly more available to the lungs than $CdCl_2$, while CdS retention was lower. The reason for the observed differences in behavior of the various cadmium compounds should be examined in future studies.

Acknowledgements

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#Cadmium oxide#

~~CdO~~ Toxicity: Macromolecular Binding of Cadmium, Zinc, and Copper in the Fibrotic Rat Lung

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~~The~~ Univ~~ersity of~~ Cincinnati Coll~~ege of~~ Med~~icine~~, Dep~~artment of~~ Environ~~mental~~ Health, Cincinnati, Ohio

ABSTRACT

Rats were exposed to CdO aerosols for 9 to 13 months at levels of about 300 μg Cd^{++}/m^3. Cadmium-, zinc-, and copper-containing protein fractions were obtained from the lungs and kidneys of these animals by dialysis and Sephadex gel chromatography. The proteins of the lung and kidney that bind these metals do not appear to be identical but have properties in common. For the first 9 months of exposure, the majority of cadmium in the lung is bound to a low-molecular-weight component resembling metallothionein, whereas the kidneys of these animals possess an additional 30% of the available cadmium bound to several polypeptides with molecular weights of between 1000 and 4500. After 13 months of exposure, no metallothionein-like fraction was observed in the lung but was observed in the kidney. Instead, 46% of the available lung cadmium was contained in the ultrafiltrate bound to lower-molecular-weight components.

Although the absorption, distribution, metabolism, toxicity, and excretion of cadmium has been the subject of extensive study,[1-2] less research has been concerned with respiratory deposition and subsequent metabolism of cadmium-containing dusts, aerosols, or fumes.[3-7] However, the relationship between elevated levels of cadmium in the lung and pulmonary emphysema or bronchitis has been noted for years.[8-10]

The metabolic fate of cadmium-containing compounds administered by other routes of entry[11-23] has been followed. From such investigations it has been established that, once absorbed, cadmium rapidly appears in the plasma and then shifts to the red blood cells where it associates with hemoglobin. In rats or mice, accumulation in the liver commences almost immediately[24-25] where the largest concentration binds to a low-molecular-weight protein, metallothionein, after an induction lag of several hours.[17,24-30] During the first 24 hr following an injected dose and after repeated injections, cadmium has also been found associated with high-molecular-weight proteins in liver and kid-

ney[17,19,26-28] which to date have been little characterized structurally. The high-molecular-weight protein–cadmium association in experiments with repeated doses has been postulated as representing excess cadmium spillage from the sequestering metallothionein.[26] After the first day, cadmium is found in the kidney as well as in the liver, again principally bound to metallothionein. These two organs accumulate the bulk of the metal administered by injection or the oral route with very little (about 1%) being distributed to the lungs.[1,12,25] In one chronic inhalation study, pulmonary absorption was calculated as representing 30% of that inhaled, and only 10% of the total cadmium recovered from the lung, liver, and kidney remained in the lung.[1,6]

This work has been undertaken to evaluate the response of the lung to cadmium oxide aerosols since studies relating exposure to cadmium with lung disease have not been followed by more detailed work directed toward elucidating the molecular mechanisms of toxicity. Cadmium was measured after varying exposure periods and located with respect to its subcellular distribution and protein association. Its distribution among the different proteins of the lung was compared with that occurring simultaneously in the kidney. It was expected that inhaled cadmium would be bound to some proteins bearing structural similarities to each other as well as to those isolated from animals given cadmium by other routes. Since at least the protein metallothionein, whether extracted from the liver or kidney in a variety of hosts[25-27,31], has been demonstrated to be remarkably similar in amino acid composition and metal binding, this assumption seemed reasonable. This paper presents data identifying rat lung and kidney cadmium-binding proteins in terms of their molecular weights and metal compositions at moderately advanced stages of lung fibrosis as measured by light and electron microscopy.

MATERIALS AND METHODS

Animals

Each experimental group was composed of 15 control and 15 exposed white Sprague–Dawley rats (Laboratory Services) that were 3 months old at the commencement of the inhalation experiments. Body weights commenced at a mean of 330 ± 10 g (±SD) and were 515 ± 50 g (±SD) at the time of death. The animals were maintained in stainless-steel cages in air-conditioned quarters on standard laboratory chow (Purina) with tap water *ad libitum*.

Inhalation Chambers and Aerosol Generation

The animal exposure chambers had an internal volume of 12 ft^3 with a conical top feed and bottom exit. The aerosols were generated by passing nebulized cadmium acetate through a 600°C oxidation furnace. The effluent airstream was cooled by a series of condensers so that the final temperature entering the chamber ranged from 35° to 40°C (Ref. 31). The effluent from the

chamber was passed through an absolute filter before venting. During the exposure periods, aerosol particles in a known volume of air from the exposure chamber were collected on Millipore filters for metal analyses by atomic-absorption spectrophotometry. The size distribution of the aerosol in the chamber was measured with a seven-stage Andersen impactor equipped with a 47-mm Type AA, 0.8-μm Millipore backup filter[32] (mass median aerodynamic diameter = 0.15 μm, σg = 2.53). Atomic-absorption spectrophotometry was used to analyze all stages for metals. The chemical composition of the particles was verified by X-ray analysis and electron spectroscopy for chemical analysis (ESCA). In solution, CdO is insoluble except in the presence of acids or ammonium salts.[33]

Inhalation Experiments

The inhalation procedures used were previously established in these laboratories.[31,34,35] Groups of 15 animals each were housed within the chambers in compartmentalized stainless-steel racks for the duration of the exposure period, after which they were returned to their regular quarters. Exposure periods lasted 7 to 8 hr per day, 5 days per week, for a total duration of 9 to 13 months. The mean chamber concentration for each exposure period was 347.5 ± 75 (SD) μg Cd^{2+}/m^3 and 282.1 ± 95.2 (SD) μg Cd^{2+}/m^3, respectively. The same number of control rats for each experiment were maintained in a laminar air-flow apparatus for the duration of the experiment. On the basis of a respiratory clearance of 0.01026 m^3/hr times the number of hours in the chamber, these two groups have inhaled 4604.8 and 5487.7 μg Cd^{2+}/rat, respectively.[35] At pulmonary compartment deposition rates of 0.2 to 0.3 of that inhaled, the calculated amount of Cd^{2+} deposited was 1151.2 μg for the 9-month exposure and 1371.9 μg for the 13-month exposure. The cadmium recovered from the lung was considered a direct reflection of that absorbed after deposition, whereas kidney cadmium was assumed to also include the fraction absorbed after ingestion. The equilibrium concentration for the lung was about 130 μg Cd^{2+} per animal.[35] After exposure of 13 months, the kidney concentration had not reached an equilibrium value.

Reagents and Glassware

All chemicals used for analyses were ultrapure or of reagent grade. All water used was triple distilled in a glass apparatus. All glassware was boiled in aqua regia, followed by rinsing in distilled water, soaked in 1% (w/v) ethylenediaminetetraacetic acid disodium salt (EDTA), and rinsed again 5 to 10 times.

Buffers [composed of 0.25M sucrose and 0.001M 2-amino-2-(hydroxymethyl)-1,3-propanediol (Tris), pH 7.4; 0.02M Tris, pH 8.6; and 0.001M Na_2CO_3, pH 7.4] were prepared on the day of use. Concentrated stock solutions of the metals and all other solutions were prepared as previously described.[34]

Metal Analyses

Analyses were performed on a Perkin–Elmer 403 atomic-absorption spectrophotometer equipped with a Boling triple slot burner and an air–acetylene flame. Sensitivity of the instrument for cadmium, zinc, and copper was 0.01 ppm at 1% absorption. The detection limit, under the experimental conditions, was 0.02 μg/ml for all three metals.

All supernatant samples were digested with 24% tetramethylammonium hydroxide in methanol before analyses. Digestion required 1 hr at 60°C in a shaking incubator at a 1:50 (w/v) ratio of sample to base. Reagent blanks and standard curves were analyzed concurrently. External standards were used.

Preparation and Fractionation of Tissue

With the use of a previously established technique,[35] anesthetized rats were opened and their lungs perfused through the heart with the sucrose–Tris buffer (pH 7.4) to remove the blood. The lungs were then washed 5 times with a 10-ml buffer via tracheal cannulation to remove alveolar macrophages, lung surfactant, and any remaining cadmium oxide particles,[36–38] after which they were stripped of the bronchi, rinsed, weighed, pressed, and homogenized (see "Results and Discussion"). Kidneys were rinsed, weighed, and transferred directly to the cold sucrose–Tris–HCl homogenization medium. The respective organs for each experiment were pooled before homogenization and fractionation. For some experiments the organs were frozen and stored at −20°C before homogenization.

The homogenization and fractionation procedure was an adaptation of standard methods.[7–37,39–42] For each preparation the organs from five animals were homogenized in 5 volumes of the above-mentioned sucrose–Tris–HCl buffer followed by centrifugation at 12,100 *g* for 30 min and 1000,000 *g* for 60 min to remove the subcellular components. The supernatants from the centrifugation were either lyophilized or subjected to ultrafiltration before further treatment. The final supernatant fractions were usually analyzed immediately for metals but could be stored at −20°C without alteration in their metal concentrations.

Ultrafiltration

Concentration to one-third of the original volume was performed under nitrogen at 50 psi at 4°C in a thin channel separator equipped with a UM-2 filter (molecular weight cutoff, 1000). The final ultrafiltrate (about 15 ml) was rinsed from the filter with 3 by 1 ml buffer and applied directly to the first column (Sephadex G-75).

Dialysis

Sodium carbonate buffer (0.001 M), pH 7.4, was used for dialysis at 4°C. The ratio of buffer to supernatant was maintained at 20 : 1. The buffer was chang

three times during a 27-hr period. The cellulose dialysis tubing (molecular weight cutoff, 3500) was pretreated to remove contaminating metal ions.[29,30] Larger pore tubing (molecular weight cutoff, 6000 to 8000) was used in a second series of experiments following the first series (see "Results and Discussion"). For the experimental group exposed to CdO aerosols for 13 months, the original protocol for dialysis was altered to include the use of the ultrafiltration apparatus to dialyze the supernatants. In this set, after centrifugation, the soluble extract was concentrated and the ultrafiltrate was dialyzed twice in succession within the same system with approximately 20 volumes of the buffer at 50 psi.

GEL FILTRATION EXPERIMENTS

Estimation of Molecular Weights

For the estimation of molecular weights of the metal-binding proteins, samples were chromatographed at 4°C on Sephadex G-200, G-100, G-75, and G-50 in columns equipped with flow adaptors for ascending and descending chromatography. The respective bed volumes were: 215 ml, 254 ml, 377 ml, and 44 ml. Tris–HCl buffers (0.02*M*, pH 8.6 and 7.6) were used at flow rates of 6 to 30 ml/hr depending on the gel, and fractions of 3 to 6 ml were collected. Reference samples (about 1% of the bed volume) were 0.2% in blue dextran and contained 0.2 to 4 mg/ml each of two of the relevant reference proteins. The seven reference proteins used were (1) thyroglobulin, (2) catalase, (3) aldolase, (4) ovalbumin, (5) chymotrypsinogen A, (6) ribonuclease A, and (7) insulin. A cadmium glutathione complex was also used for the Sephadex G-50 column. Two to four reference proteins were fractionated on each column preceding each filtration experiment. A standard curve was derived from a plot of log molecular weight vs. elution volumes.[43] Elution volumes (V_e) were monitored at 280 and 254 nm.

Before each experiment the columns were treated with the elution buffer containing (0.001*M*) *ortho*-phenanthroline to remove contaminating metal ions.

Isolation of the Cd^{2+}-Binding Proteins of the Lung and Kidney

Samples of the nondiffusible, nonultrafilterable material from lung or kidney were applied to a column packed with Sephadex G-75 (fine grade) equilibrated with (0.02*M*) Tris–HCl buffer, pH 8.6. The effluent from the column was monitored at 253.7 nm and collected in 3- to 5-ml aliquots. Samples were run from bottom to top at a flow rate of 30 ml/hr. All experiments were performed at 4°C. The fractions were analyzed for metal and protein[44] where necessary and were pooled according to the metal-ion elution pattern(s). The pooled fractions were concentrated with an ultrafiltration unit equipped with a UM-2 or UM-10 filter

(depending on the molecular weight of the fraction) before subsequent reapplication on the succeeding columns. Gel filtration experiments conducted on Sephadex G-50 were performed with 0.02M potassium phosphate buffers, pH 7.4. All fractions that were not concentrated and reapplied to the succeeding column(s) were lyophilized and stored at −20°C. The results of several filtration experiments will be discussed.

Light Microscopy

Tissue samples from the two groups of animals (three experimental animals and three controls per group) exposed to CdO for 9 and 13 months were taken for evaluation.

For routine examinations, tissues were fixed in formalin, embedded in paraffin wax, and sectioned at 8 μm. The sections were stained with hematoxylin and eosin.

RESULTS AND DISCUSSION

There was a prolonged latent period before fibrosis of the lung was appa by light microscopy.[4,5] For this paper, measurements were performed on groups of animals exposed, respectively, to CdO aerosols for 9 and 13 months, as well as on their controls. There were no noticeable pathological changes due to the perfusion/lavage treatment of the lungs. At the light microscope level, the present observations correspond to those previously described.[4,5] More specifically, in the lung, fibrosis of the wall was present, extending into the adjacent alveoli. There was also infiltration by lymphocytes. Some macrophages were scattered throughout the alveoli. One rat showed a more advanced fibrosis. Occasionally proliferative lesions were seen in all exposed lungs. These consisted of small papilloma-like excrescences into the lumen of the terminal bronchiole. They were made up of fibrous tissue with lymphocytic infiltrates. The surface was covered by flat epithelium. Significant fibrosis of the pleura was absent. Lungs of the control rats showed the usual histologic structure without pathologic alterations.

The microscopic examination of the lung of all animals submitted after 13 months' exposure revealed an increase in the fibrosis of the respiratory bronchioles when compared with animals exposed for 9 months. Special stains for fibrous tissue and muscle tissue showed that the fibrous tissue was collagenous. No additional significant differences were present.

The microscopic examination of the kidneys using H & E stained sections revealed focal interstitial nephritis with rare foci of fibrosis after 9 months exposure. No additional changes were observed after 13 months that could be attributed to CdO. A slight thickening of the Bowman's capsule was observed in all animals, but it is a common feature in rats at 15 to 16 months.

Previous work in these laboratories has established that, once animals are exposed to the aerosols for several weeks, the majority of the cadmium is associated with the soluble supernatant of the cells.[35] After 9 months, cadmium levels begin to reach a plateau in the lung. The approach to equilibrium concentrations of cadmium in the lung after this period has been tentatively correlated with the appearance of lung pathology, which was only evident after this exposure. Light microscopic examination of the kidneys of these animals indicated only isolated pathological changes, and equilibrium concentrations were not apparent in the kidney even after 13 months' exposure.

Biochemical fractionation of both organs has demonstrated some similarities and differences. Half the homogenates from 10 lungs and 10 kidneys were used for the preparation of the material subsequently described.

Dialysis experiments lasting 24 hr were performed on the 100,000 × *g* supernatant fractions of both lung and kidney from the 9-month exposure period. For this exposure period, there were maximum losses of about 10 to 50% of the cadmium, 18% of the available zinc, and 30 to 45% of the copper from the lung supernatant. In the kidney, similar treatment yielded a 45% loss of cadmium, a 50% loss of zinc, and a 55% loss of copper (Table 1).

When the dialysates were separated on Sephadex G-75, the total recovery was 90 to 100% of that applied. The elution profiles of the supernatants from a 9-month exposure group are shown in Figs. 1(a) and 2(a). Chromatography of these dialysates indicated that cadmium was primarily associated with a low-molecular-weight component of about 12,500 in both organs (V_e = about 325 ml). A distinct difference in the relative ratios of metals was observed between the lung and kidney for this fraction. In the lung the cadmium/zinc/copper mole ratio was 38 : 8 : 1, whereas in the kidney a considerable redistribution of the metals, presumably through metabolic processes, was evident in the respective mole ratios of 5.3 : 1 : 4.6 for the same fraction. These ratios are expected to change somewhat with further purification. The apparent cadmium/zinc/copper mole ratio in the kidney may be a reflection of the presence of two isostructural proteins as has been previously observed.[30] In the lung, this molecular-weight fraction represented 83% of the cadmium, 21% of the zinc, and 38% of the copper put on the column. For the kidney, 45% of the cadmium, 8% of the zinc, and 42% of the copper put on the column were recovered in this fraction. The molar ratios of titratable sulfhydryl groups[29] to metals in this fraction were as follows for the respective organ fraction:

	$\frac{\mu M\ (SH)}{\mu M\ Cd}$	$\frac{\mu M\ (SH)}{\mu M\ Zn}$	$\frac{\mu M\ (SH)}{\mu M\ Cu}$	$\frac{\mu M\ (SH)}{\mu M\ (Cd + Zn + Cu)}$
Lung	2.59	13.89	65.97	2.11
Kidney	4.36	21.20	5.12	2.12

A higher-molecular-weight cadmium-containing component was observed in the lung. This fraction represented 10% of the total cadmium, 40% of the zinc,

TABLE 1

REPRESENTATIVE YIELDS OF CADMIUM-BINDING COMPONENTS IN LUNG AND KIDNEY AFTER 9 MONTHS' CdO INHALATION EXPOSURE

Fraction	Controls				Exposed			
	Cd, %	Zn, %	Cu, %	Protein, %	Cd, %	Zn, %	Cu, %	Protein, %
LUNG								
Supernatant	100	100	100	100	100	100	100	100
Supernatant after dialysis vs. Na_2CO_3	<limit	53	84.5	82.1	74.3	81.7	56.3	102.3
Sephadex G 75 Filtration								
Fraction 1, V_e = 120 to 180 ml	<limit	9.3	13.3	66.2	7.5	32.3	12.8	84.7
Fraction 2, V_e = 180 to 230 ml	<limit	8.6	16.3	5.0	1.9	11.7	20.6	11.9
Fraction 3, V_e = 230 to 280 ml	<limit	6.9	17.1	3.0	4.7	17.0	21.5	3.3
Fraction 4, V_e = 280 to 370 ml	<limit	<limit	<limit	3.1	51.3	1.4	0.6	2.3
Fraction 5, V_e = 370 to 475 ml	<limit	28.2	37.6	4.7	0.9	5.2	0.1	0.1

KIDNEY								
Supernatant	100	100	100	100	100	100	100	100
Supernatant after dialysis vs Na_2CO_3	100	44.6	89.5	74.4	55.0	48.7	45.3	70.8
Sephadex G-75								
Elution								
Fraction 1, V_e = 120 to 180 ml	6.1	20.6	3.8	50	4.5	16.4	5.2	3.75
Fraction 2, V_e = 180 to 230 ml	2.8	11.5	11.0	10.3	6.0	6.0	6.1	1.1
Fraction 3, V_e = 230 to 280 ml	19.6	5.9	16.6	3.0	25.4	3.7	19.1	25.3
Fraction 4, V_e = 280 to 370 ml	71.5	6.5	57.9	6.2	3.9	1.9	2.9	17.4
Fraction 5, V_e = 370 to 475 ml	<limit	<limit	<limit	4.9	3.4	20.6	1.0	23.1

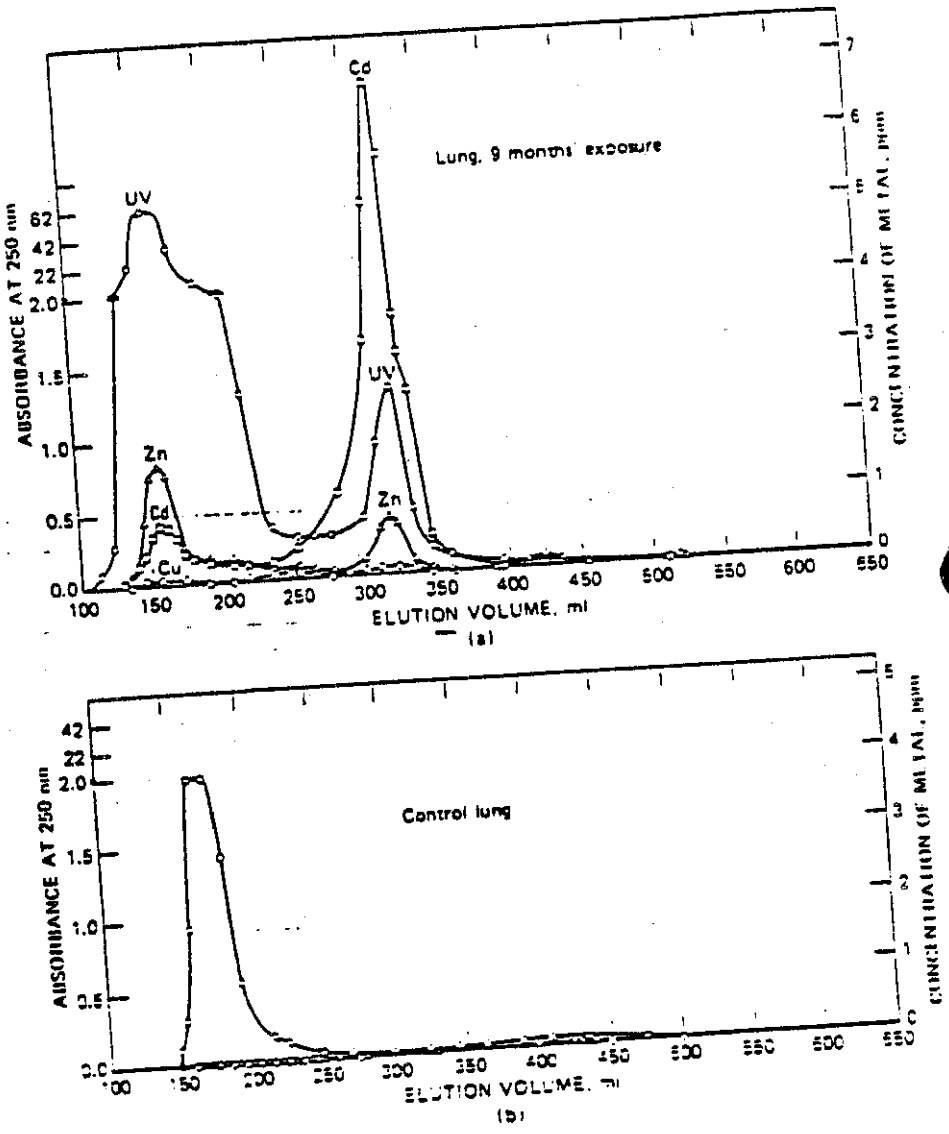


Fig. 1 Sephadex G-75 gel elution profiles of the supernatant fraction from the lungs of rats (a) exposed to CdO aerosols (347.5 mg/m^3) for 9 months and (b) their paired controls. The column (82 by 2.5 cm) was eluted at 4° C with 0.02M Tris–HCl buffer, pH 8.6, at flow rates of 30 ml/hr. Fractions (6 ml) were collected and analyzed for Cd^{2+} (□), Zn^{2+} (△), Cu^{2+} (○), and protein (○), optical density at 250 nm. Both supernatants were dialyzed at 4°C before gel filtration. The Cd^{2+} concentration of the dialysates were (a) 20.55 μg/ml and (b) 0.008 μg/mL

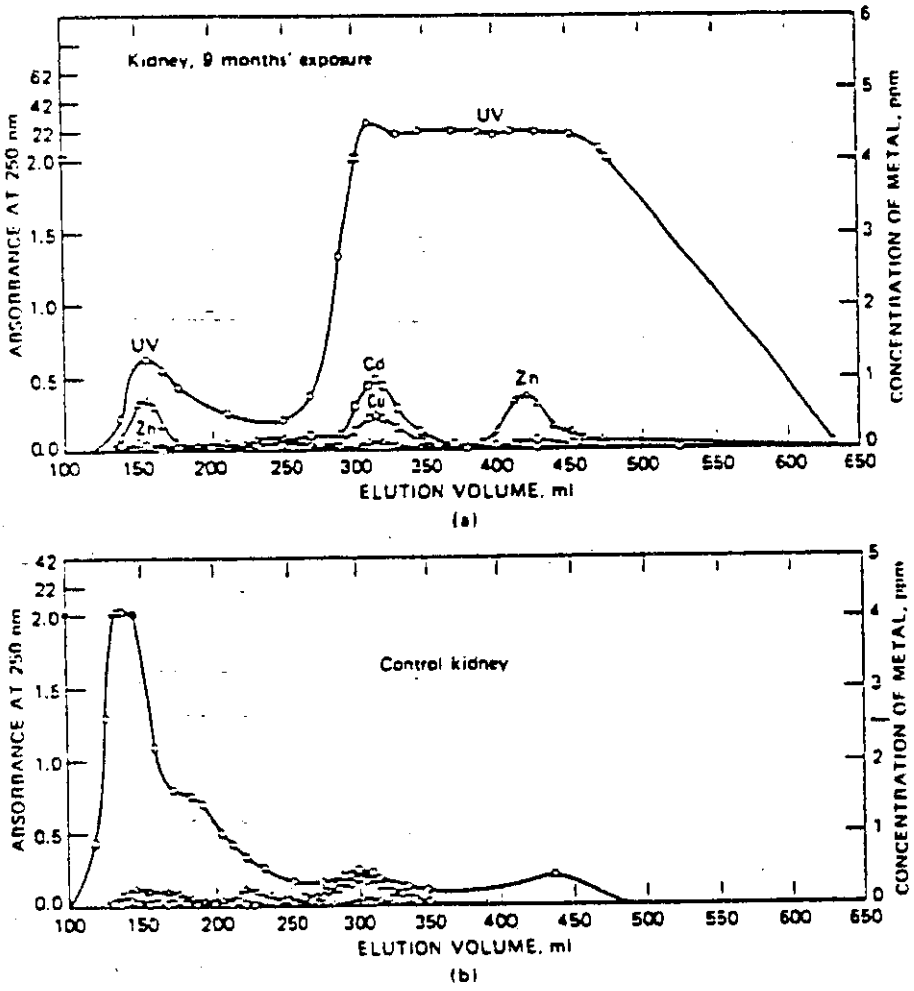


Fig. 2 Sephadex G-75 gel elution profiles of the supernatant fraction from the kidneys of rats (a) exposed to CdO aerosols (347.5 mg/m^3) for 9 months and (b) their paired controls. The column (82 by 2.5 cm) was eluted at 4°C with 0.02M Tris–HCl buffer, pH 8.6, at flow rates of 30 ml/hr. Fractions (6 ml) were collected and analyzed for Cd^{2+} (□), Zn^{2+} (△), Cu^{2+} (○), and protein (·), optical density at 250 nm. Both supernatants were dialyzed at 4°C before gel filtration. The Cd^{2+} concentration in the dialysates were (a) 5.55 μg/ml and (b) 3.22 μg/ml.

and 23% of the copper. The molecular weight was 90,000 or above since the component eluted close to the void volume. A similar component was present in the kidney in lesser quantities. Cadmium has been previously observed to be bound to high-molecular-weight components in the liver following high injection levels.[26] Whether this fraction represents "spillage" from the sequestering metallothionein or initial binding to a large protein before synthesis of

metallothionein[19] cannot be determined at present. The synthesis of almost exclusively cadmium–thionein in the kidneys of rabbits has been reported.[25] It is interesting that, under the conditions of the present experiment, which represent chronic exposures, a fraction similar to cadmium–thionein (by virtue of its molecular weight, its metal and sulfhydryl concentration, and its ultraviolet extinction coefficient ratio) was only observed in the lung. In the kidney the analogous fraction contained appreciable quantities of copper.

Dialyzable material from the kidney representing 30% of the total supernatant Cd^{2+} and 20% of the total protein was chromatographed on a Sephadex G-25 column. The cadmium-binding fractions separated into two peaks: fraction 1, eluting in the void volume (6% total supernatant cadmium) and fraction 2, eluting at 32 ml (20% total supernatant cadmium). Both fractions were concentrated and rechromatographed on G-50 (Fig. 3), where additional separation occurred.

Figure 3(a) is the elution profile of the higher-molecular-weight fraction 1 from G-25. Two cadmium-binding components are apparent. The first component, with a molecular weight of >10,000, has $\lambda_{max.}$ at 275 and 405 nm ($\epsilon_{max.}$, 405). The cadmium recovered was 30% of that put on the column (2 to 2% total supernatant cadmium). The second component, with V_e = 45 ml and a molecular weight of about 4500, has $\lambda_{max.}$ at 225 and 273 nm ($\epsilon_{max.}$, 225) and appears to be a binary mixture since the $\lambda_{max.}$ at 273 nm peaks at V_e = 49 ml whereas [Cd] is at a maximum at V_e = 44 ml. The cadmium recovered was 60% of that put on the column (about 3% total supernatant cadmium).

Similar ultraviolet absorbing components appear in the elution profile shown in Fig. 3(b), which originated as the lower-molecular-weight fraction 2 from G-25. The third component, eluting at 64 ml (molecular weight of about 700) contains 25% of the cadmium recovered from the column ($\lambda_{max.}$, 225, 264, and 290; $\epsilon_{max.}$, 225), and, on the basis of its ultraviolet spectrum, it appears to be a purified constituent of the binary mixture eluting at 50 ml in Fig. 3(a).

Fractionation of control-animal organs was identical to that of the preceding description. After a 24-hr dialysis experiment, 45% of the available zinc and 15% of the available copper were removed from the supernatant (100,000 × *g* fraction) of the control lung. The total metal concentration at this point was 0.18 μg/mg of protein. In the kidney, similar treatment yielded no loss of cadmium, a 55% loss of zinc, and a 10% loss of copper (Table 1). The total metal concentration was 0.67 μg/mg of protein at this stage.

The Sephadex G-75 elution profiles for the control animals are shown in Fig. 1(b) and 2(b). The vast majority of the protein in control lung and kidney elutes in the void volume of the column, although a small amount of material in the 12,000-molecular-weight range is observed in the kidney.

Further fractionation of the high-molecular-weight lung proteins on Sephadex G-100, with similar treatment to that described in Fig. 4(b) (flow rate, ml/hr), yielded two peaks: (1) a low-molecular-weight (<25,000) component that represented the majority of the protein and (2) a high-molecular-weight

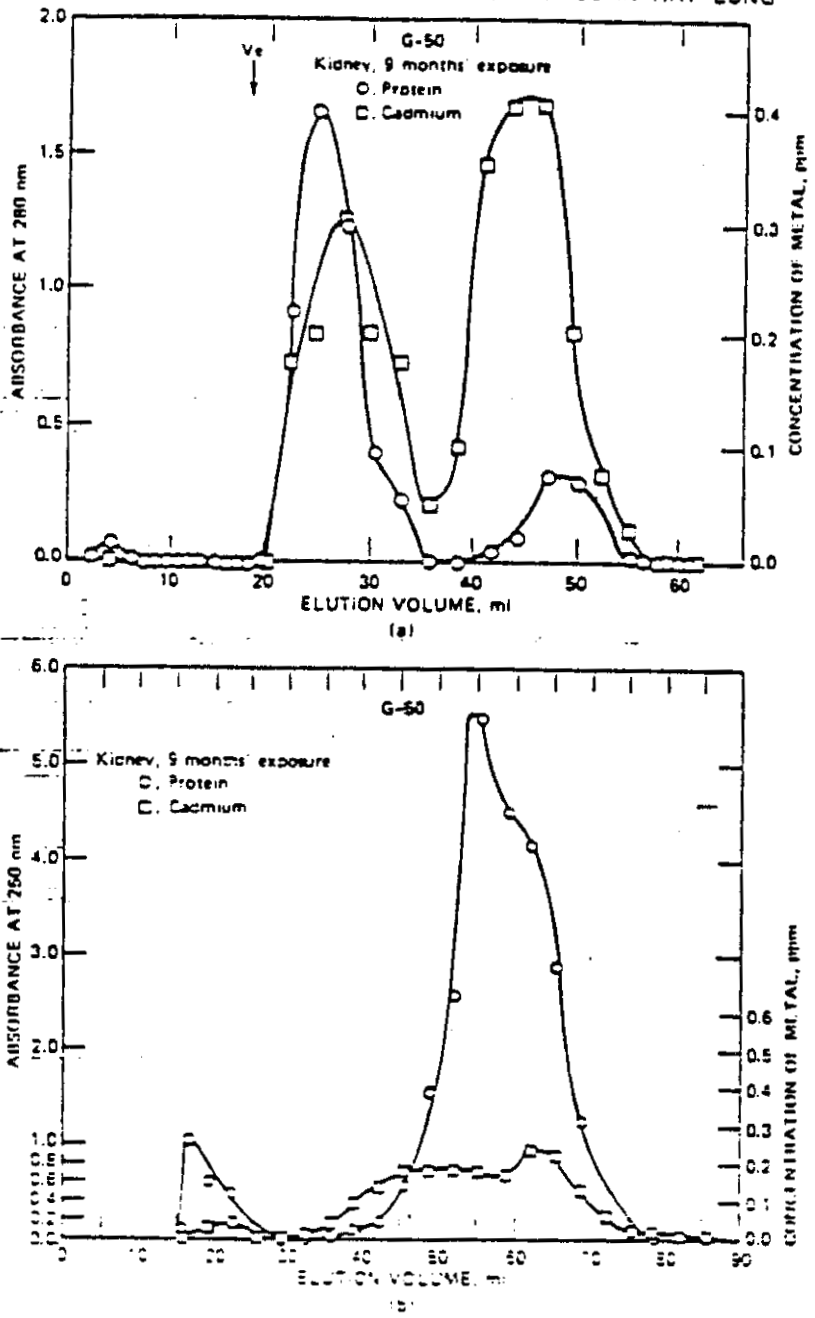


Fig. 3 Sephadex G-50 separation of dialyzable components from the kidneys of rats exposed to CdO for 9 months. The column dimensions were 1.5 cm by 30.0 cm. Elutions were carried out at 4°C with (a) 0.025M phosphate buffer pH 7.1 and (b) 0.025M Tris–HCl buffer pH 7.3 at flow rates of 18 ml/hr (3 ml/fraction). (a) Material collected from fractions 4 to 6 of the preceding G-25 filtration (4.67 μg Cd^{2+}/ml). (b) Material collected from fractions 7 to 15 at the preceding G-25 filtration (11.0 μg Cd^{2+}/ml) (see text).

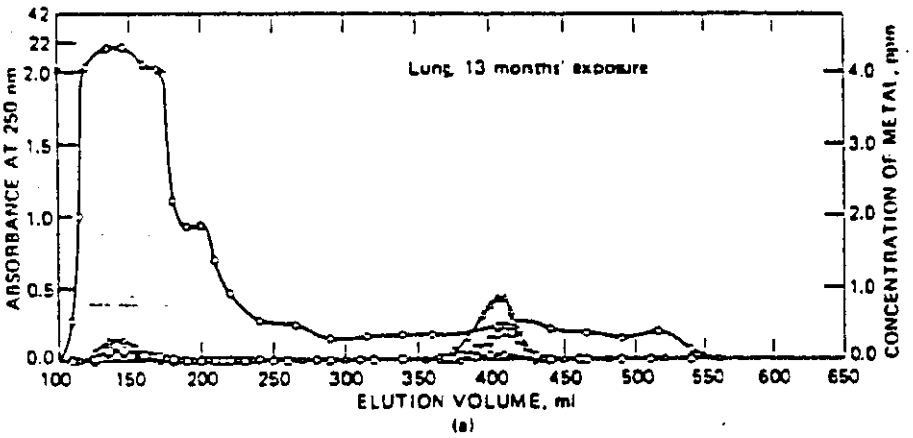
(>150,000) component that was present in small quantities. The kidney proteins have not been purified on G-100 to date.

Because the interstitial disease observed by light microscopy was only moderately advanced at the end of 9 months, one experimental group was left in the chamber for 13 months. Fractionation of these organs was identical to that of the preceding description except that dialysis was performed through the use of an ultrafiltration apparatus equipped with a UM-2 membrane (molecular weight cutoff, 1000).

Dialysis via ultrafiltration of the lung-soluble supernatant resulted in 60% of the available cadmium, 40% of the available zinc, and 25% of the available copper being removed (Table 2). The metal concentration in the remaining dialysate was 0.27 μg/mg of protein. Identical treatment of kidney supernatant removed only 18% Cd^{2+}, 20% Zn^{2+}, and 10% of the available Cu^{2+} (Table 2). The metal concentration in the remaining dialysate was 0.74 μg/mg of protein. The G-75 and G-100 elution profiles for the dialysates of each organ are shown in Figs. 4 and 5. As can be deduced from Table 2, the total recovery of Cd^{2+} from the G-75 column was 58% of that applied for the lung and 100% of that applied for the kidney.

The most remarkable change noted in the lung supernatant was the virtual absence of a fraction with a molecular weight corresponding to that of metallothionein. The two cadmium-binding fractions present correspond to molecular weights of >150,000 (void volume elution) and 3900 (fractions 1 and 4, respectively, in Table 2). Chromatography of the first on G-100 [Fig. 4(b)] resulted in further separation of this high-molecular-weight fraction into two metal-containing components, each representing 5 to 6% of the original supernatant cadmium if we adjust the figures to account for the low G-75 column recovery. Fraction 4, eluting at 410 ml from G-75, represented 22% of the total cadmium in the supernatant and had a molecular weight of about 4000 with ε250/280 = 1.5, as did the small fraction eluting at 425 ml from similar treatment of the 9-month lungs [see Fig. 1(a)].

The G-75 gel filtration of the kidney dialysate separated approximately the same number of metal-binding components as were observed at 9 months' exposure, although the relative proportions were altered [Fig. 5(a)]. After 13 months, 44% of the available Cd^{2+}, 32% of the available Cu^{2+}, and 1% of the available Zn^{2+} were recovered in the low-molecular-weight metallothionein-like fraction 3 (molecular weight of 10,500 with ε250/280 = 1.6). Table 2 lists the representative recovery of each metal and the total protein in the individual fractions from the columns. Thus fraction 1 (V_e = 135 to 223 ml) contained 18%, fraction 2 (V_e = 223 to 290 ml) contained 10%, and fraction 4 (V_e = 360 to 475 ml) contained 9% of the total supernatant cadmium. Fraction 1 was concentrated and further separated on Sephadex G-100 [Fig. 5(b)]. Cadmium recovery was 85% of that applied. Whereas the lung appears to possess two high-molecular-weight metal-binding proteins [Fig. 4(b)], the kidney appears to contain 3 or possibly 4, together totaling 16% of the available Cd^{2+}. The small



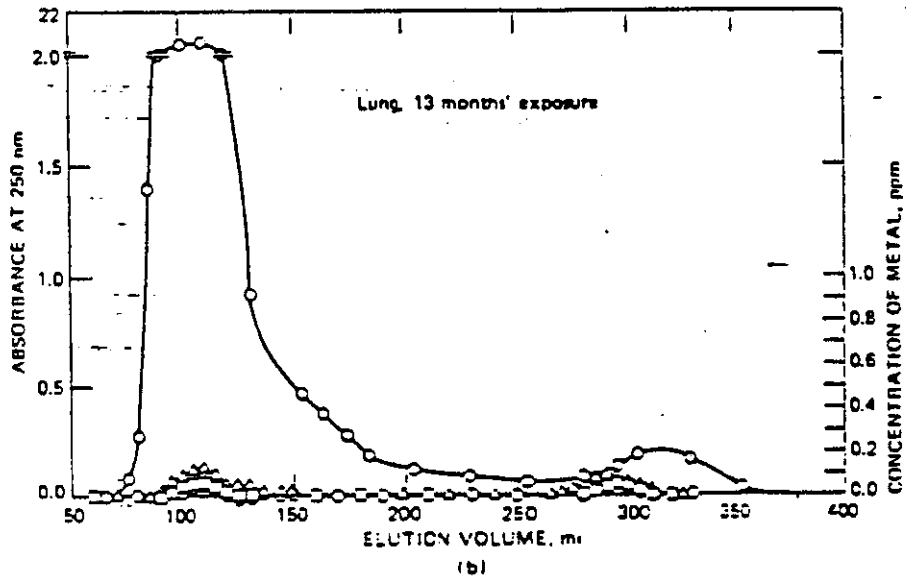


Fig. 4 Sephadex gel elution profiles of the supernatant fractions from rat lungs eluted at 4°C with 0.02M Tris–HCl buffer, pH 8.6. Dialysis was performed at 4°C before gel filtration. Fractions collected were analyzed for Cd^{2+} (□), Zn^{2+} (△), Cu^{2+} (○) and protein (▽), optical density at 250 nm. (a) Dialysate (1.88 μg Cd/ml) applied to G-75 column (82 by 2.5 cm), flow rate 30 ml/hr, 5 ml/fraction. (b) Fraction 1 (116 to 235 ml elution) from G-75 column (0.37 μg Cd/ml), applied to Sephadex G-100 column (64 by 2.5 cm), flow rate 6 ml/hr, 5 ml/fraction. The exposure level was 289 $\mu g/m^3$ for 13 months.

TABLE 2

REPRESENTATIVE YIELDS AND DISTRIBUTION OF METAL BINDING COMPONENTS IN LUNG AND KIDNEY AFTER 13 MONTHS' CdO INHALATION EXPOSURE

Fraction	Exposed lung				Exposed kidney			
	Cd, %	Zn, %	Cu, %	Protein, %	Cd, %	Zn, %	Cu, %	Protein, %
Supernatant	100	100	100	100	100	100	100	100
Supernatant after dialysis vs. Na_2CO_3	38.6	60.8	74.4	76.5	82.2	78.4	92.4	98
Sephadex G 75 Filtration								
Fraction 1, V_e = 116 to 190 ml = 135 to 223 ml	7.2	11.0	30.3	59.8	18.4	13.0	12.7	57.8
Fraction 2, V_e = 190 to 216 ml = 223 to 290 ml	<limit	<limit	8.4	9.9	10.2	8.8	11.7	17.7
Fraction 3, V_e = 240 to 360 ml = 290 to 360 ml	<limit	<limit	<limit	1.6	44.2	1.4	32.4	1.7
Fraction 4, V_e = 360 to 435 ml = 360 to 475 ml	15.2	31.2	22.7	0.6	9.4	24.9	<limit	6.7

Fraction 5,								
V_e = 435 to 560 ml	<limit	<limit	<limit	0.7				
= 475 to 550 ml					<limit	<limit	<limit	5.9
Sephadex G-100								
Filtration,								
Fraction 1 above								
Fraction 1,								
V_e = 91 to 131 ml	3.4	6.5	6.8	31.7				
= 70 to 150 ml					11.9	9	9.2	35.0
Fraction 2,								
V_e = 131 to 200 ml	<limit	1.1	3.4	8.1				
150 to 200 ml					0.5	<limit	1.2	1.0
Fraction 3,								
V_e = 200 to 274 ml	<limit	<limit	<limit	2.0				
= 200 to 245 ml					<limit	<limit	<limit	0.5
Fraction 4,								
V_e = 274 to 304 ml	2.7	3.8	1.7	5.3				
= 245 to 290 ml					5.3	3.9	1.2	0.7
Fraction 5,								
V_e = 304 to 360 ml	<limit	<limit	<limit	6.2	<limit	<limit	<limit	0.7

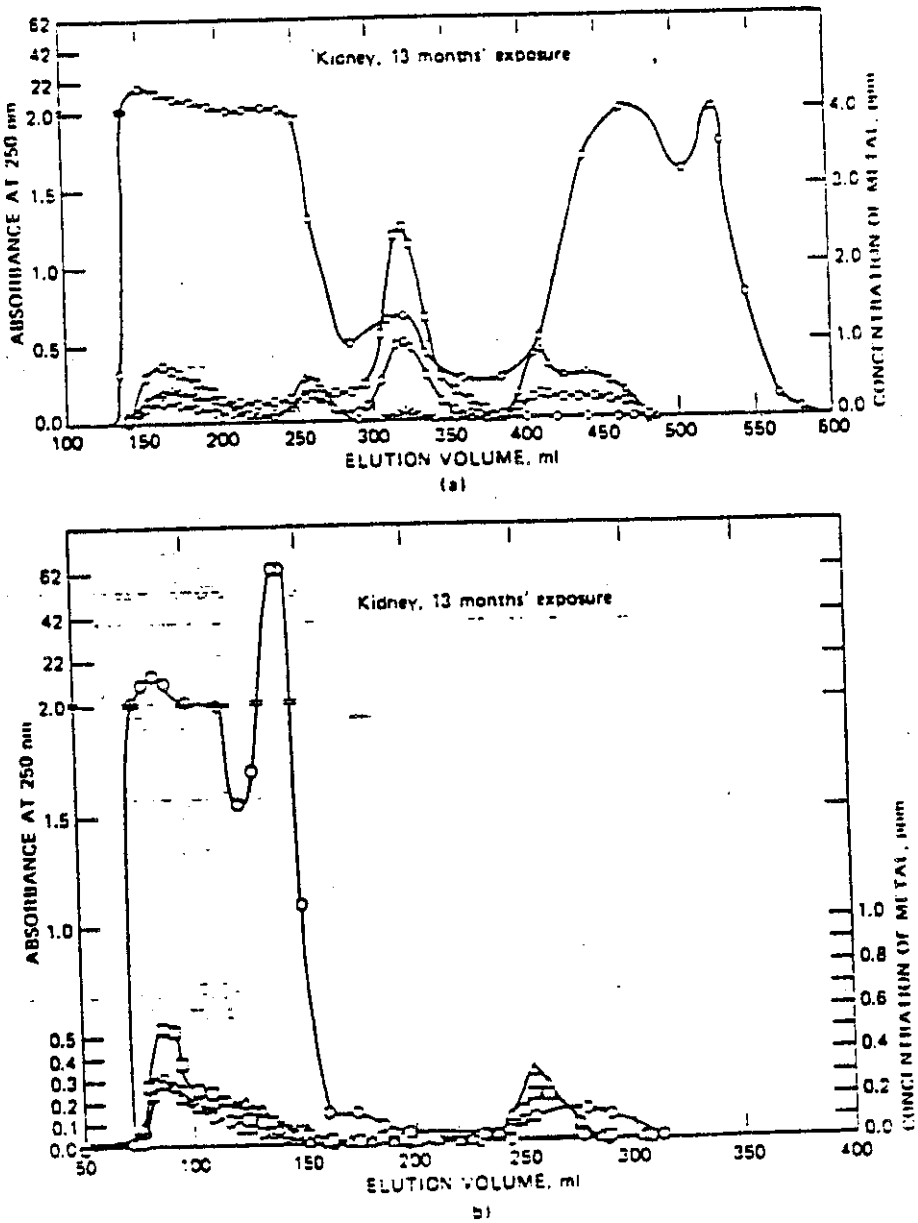


Fig. 5 Sephadex gel elution profiles of the supernatant fractions from rat kidneys eluted at 4°C with 0.02M Tris–HCl buffer pH 8.6. The supernatant was dialyzed at 4°C before gel filtration. Fractions collected were analyzed for Cd^{2+} (□), Zn^{2+} (△), Cu^{2+} (○), and protein (○), optical density at 250 nm. (a) Dialysate (5.37 μg Cd/ml) applied to G-75 column (82 by 2.5 cm), flow rate 30 ml/hr, 5-ml fractions collected. (b) Fraction 1 (135.5 to 223.5 ml elution) from G-75 column (4.30 μg Cd/ml), applied to G-100 column (64 by 2.5 cm), flow rate 4 ml/hr, 3-ml fractions collected. The exposure level was 289 $\mu g/m^3$ for 13 months.

fraction with an elution volume of about 250 to 300 ml in both Figs. 4(b) and 5(b) corresponds to a molecular weight of <25,000.

We call attention to the pathology of the lungs from this latter group of animals, which were previously described as being in a definitive state of fibrosis. Because the lungs are quite fibrotic, homogenization of the tissue is very difficult and the yield of extractable soluble protein is relatively low. Likewise, the cadmium concentration (2.36 μg/ml) in the soluble supernatant is much lower than that measured in the lungs of animals exposed for only 9 months (5 to 13 μg/ml). This does not explain, however, the absence of low-molecular-weight (10,000 to 12,000) components or the presence of a substantial percentage of dialyzable cadmium. Further work is in progress.

ACKNOWLEDGMENTS

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Organ Distribution and Protein Binding of Cadmium in Autopsy Material from Heavy Smokers

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Male heavy smokers were autopsied within 3 days postmortem. Samples from kidney, liver, and lung were taken for analysis of cadmium levels and degree of protein binding within the cytosolic fraction. The levels in lung, liver, and kidney were 0.50 ± 0.35 ($\bar{X}$ ± SEM), 2.21 ± 0.63, and 17.4 ± 8.8 μg cadmium/g wet weight tissue, respectively. In liver and kidney, approximately 75% was bound to a low-molecular-weight protein whereas the corresponding figure for the lung cytosolic fraction was 56%, a difference being statistically significant ($P < 0.05$). After concentration of the low-molecular-weight cadmium-binding protein(s) (CdBP) by ultrafiltration and preparative isoelectric focusing in a granulated gel, the cadmium appeared in one single band with pI values of 5.8 (lung and liver) and 6.0 (kidney), respectively. It is therefore concluded that human lung exposed to cadmium, in this case via cigarette smoke, contains a CdBP, which binds cadmium. The relative degree of binding is less in lung than in liver or kidney, implicating that the metal could be more toxic to the lung than to liver or kidney, as the protein probably serves a role in detoxifying cadmium.

INTRODUCTION

Prolonged exposure to cadmium has been shown to cause accumulation of the metal mainly in the kidneys, which probably also is the main target for the toxic action (Baader, 1952; Bonnell, 1955; Kazantsis *et al.*, 1963). Pulmonary emphysema has also been shown to be developed in workers after prolonged high-dose exposure to cadmium by inhalation of contaminated air (Friberg *et al.*, 1974). One possible mechanism underlying the development of pulmonary emphysema involves proteolytic attack on the tissue by endogenous proteolytic enzymes, because proteases, instilled into the lung through the trachea, produce emphysema-like lesions (Gross *et al.*, 1965). The emphysema caused by inhalation exposure to cadmium could thus be mediated by proteolytic enzymes from cells in the lung. The studies by Henderson and collaborators have not clearly demonstrated such an effect by cadmium, however, when the metal was instillated as a solution into the trachea (Henderson *et al.*, 1979).

A protein with specific cadmium-binding ability, metallothionein, has been demonstrated mainly in liver and kidney cytosolic fractions. This protein plays a central role in the intracellular metabolism of cadmium (Nordberg *et al.*, 1971) by chelating the metal ions in the tissue, and in this way it is believed to protect sensitive metabolic functions of the cells. Cadmium-binding protein(s) similar to

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TABLE 1
INDIVIDUALS AUTOPSIED

Initials	Age (years)	Time between death and autopsy (days)	Primary cause of death
K.K.	78	1	Bronchial pneumonia
B.-O.E.	69	4	Cardiac infarction
B.L.	71	2	Pulmonary edema
ÅR.	65	3	Subarchnoidal bleeding
E.S.	78	3	Pulmonary cancer with metastases

methallothionein have been detected in syrian hamster lung (Benson and Henderson. 1980) and in several cell lines derived from pulmonary tissue (Cox and Waters. 1978; Hart and Keating. 1980; Hildebrand and Cram. 1979). The proteins have been shown to be synthesized de novo on exposure to an aerosol of cadmium chloride (Post *et al.*, 1982). An alternative explanation to that of proteolytic attack on the lung. could either be that the lungs in man do not synthesize the CdBP in lung at exposure, or that the amount is not sufficient to bind all the accumulated metal in the lungs. In both cases. the Cd^{2+} ions would be free to excert their toxic action on the tissue. The aim of the present investigation was therefore (1) to see whether man exposed to cadmium via the airways has detectable metallothionein-like proteins in the lung and (2) whether the Cd^{2+} ions persist in the lung tissue in their free or bound form. Heavy smokers were used as source for tissue specimens postmorten. as this category has an elevated body burden of cadmium due to contamination of the tobacco (Elinder *et al.*, 1976).

MATERIALS AND METHODS

Five heavy smokers autopsied at the Department of Clinical Pathology at the Linköping University Hospital were investigated. The age and cause of death are listed in Table 1. The time between death and autopsy was 3 days (mean) with a range of 1 to 4 days. The bodies were kept at +4°C until autopsy was performed. In subject E.S., who had a pulmonary cancer. the material used in this study was noncancerous. The material was frozen and kept at −20°C until processed further. A freeze-pressing technique (Edebo. 1960) was used for homogenization. A buffer containing 0.25 M sucrose, 0.01 M Tris–hydroxymethyl–aminomethane (Tris). and adjusted to pH 8.6 with hydrochloric acid. was added in equal weight to the tissue before the homogenization. The homogenate was centrifuged at 150.000*g* to isolate the cytosolic fraction of the tissue. Samples of this and the crude homogenate were saved at −20°C for later analysis of protein content and cadmium level. A sample of the cytosolic fraction of lung. liver. and kidney from each individual was applied to a 2.8 × 65-cm Sephadex G50 column. The samples were eluted with a 0.01 M Tris–HCl buffer (pH 8.6) containing 0.02% sodium azide. Samples of 11 ml were collected to later be monitored for protein. measuring the absorbance at 280 nm in a Pye–Unicam SP-500 uv spectrophotometer. The cadmium levels were determined using an Instrumentation Laboratory 551 atomic absorption spectrophotometer equipped with a graphite furnace (Instru-

mentation Laboratory 555) and an automatic sampler (Instrumentation Laboratory 254). The method gave acceptable signal-to-noise ratios down to 1 ng/ml sample. The samples from the column containing CdBP were pooled, concentrated using a Micropore UM2 ultrafilter, and later characterized further by isoelectric focusing.

Flat-bed isoelectric focusing was carried out with the use of an LKB Multiphore apparatus coupled to an LKB power supply (model 2103). Cold tap water was used in order to maintain the cooling plate and the gel at a temperature of +10°C. The electrofocusing was run in a granulated gel bed composed of 6.6% Ultrodex (LKB) and 2% carrier ampholytes (LKB Ampholines) covering a pH range of 3.5–10.0. Samples of 1.0 ml concentrated and pooled CdBP from the individuals were mixed with the gel slurry before being added to the gel plates. The electrofocusing was run for approx 22 hr at a constant power of 5.2 W with an initial voltage gradient of 20 V/cm. After completion, a grid was applied to the gel, dividing it into 30 fractions. The gel from each section was removed, vortexted in a plastic tube with 1.0 ml of distilled water, the contents were cooled to +10°C, and the pH was measured with a combined glass/calomel electrode. The gel slurry was then filtered to remove the solid matrix and the liquid phase assayed for cadmium content.

RESULTS

The individuals examined in this study all had their highest levels of cadmium in the kidneys, followed by the liver and lungs (Table 2). The kidneys also showed a larger variation in the cadmium levels than the other two organs. The levels in kidney varied between 9.1 and 30.4 μg/g wet weight tissue, while the corresponding values in liver and in lung were 1.3–2.8 and 0.2–1.1 μg/g, respectively. Figure 1 shows three individual curves from the Sephadex G50 column. Part of the cadmium eluted from the column in the high-molecular-weight protein peak, and part of it at an elution volume around 1000 ml, where no peak was found at 280 nm, indicating that the cadmium-binding protein(s) in this region were similar to metallothionein in having no aromatic amino acids. The value of the relative distribution of cadmium between the high-molecular-weight protein (HMWP) as estimated from the Sephadex G50 chromatography and the CdBP similar to metallothionein was larger in lung then liver and kidney (Fig. 1 and Table 2). The CdBP peak (Fig. 1) from each organ was concentrated and 1 ml was applied to the isoelectric focusing bed as described under Materials and Methods. A single distinct peak of cadmium binding was found in all cases, having pI values of 5.8 (lung and liver material) and 6.0 (kidney material), respectively.

DISCUSSION

The individuals autopsied in the present investigation all had a level of cadmium in kidney around 30 mg/kg wet weight and less, which is far below the 200 mg/kg reported to cause toxic reactions in the kidney (Friberg *et al.*, 1974). It is, however, comparable to levels found by others in tissue from heavy smokers, where the tobacco has been shown to cause an additional source of cadmium to the general environmental background levels (Elinder *et al.*, 1976). The material

TABLE 2

TISSUE LEVELS OF CADMIUM AND THE RELATIVE BINDING TO THE LOW-MOLECULAR-WEIGHT CdBP AND THE HIGH-MOLECULAR-WEIGHT PEAK (HMWP) ACCORDING TO GEL FILTRATION (SEE FIG. 1).

	Individual					
	K.K.	B.-O.E.	B.L.	A.R.	E.S.	Mean ± S.E.M.
Lung						
Total amount (μg g wet weight tissue)	0.29	0.20	0.51	1.09	0.41	0.50 ± 0.35
Amount bound to CdBP (%)	31	62	68	65	52	56 ± 15
Amount bound to HMWP (%)	69	38	32	35	48	44 ± 15
Liver						
Total amount (μg/g wet weight tissue)	2.63	1.32	1.79	2.56	2.76	2.21 ± 0.63
Amount bound to CdBP (%)	66	63	88	80	81	*76 ± 11
Amount bound to HMWP (%)	34	37	12	20	19	*24 ± 11
Kidney						
Total amount (μg/g wet weight tissue)	9.07	16.73	20.83	30.39	9.86	17.00 ± 8.76
Amount bound to CdPB (%)	70	84	34	72	70	*76 ± 7
Amount bound to HMWP (%)	30	16	16	28	30	*24 ± 7

* $P < 0.05$ (paired t test) compared to lung.

in this study is far too small, however, to permit any conclusions to be drawn about the role of cigarette smoking in cadmium accumulation in man. However, the aim of the investigation was to give the binding characteristics of the metal to different protein fractions in lung, liver, and kidneys.

It is evident that lung tissue, as well as liver and kidney tissues, contain a protein in the low-molecular-weight range which binds cadmium to a high extent. Using gel filtration and isoelectric focusing, the protein(s) have been shown to have a molecular weight in the range of 10,000 Da, which is similar to metallothionein, and the absence of absorbance at 280 nm indicates another similarity. The pI values of the single peaks appearing at isoelectric focusing (Fig. 2) were 5.8 for lung and liver and 6.0 for kidney cytosolic CdBP. These are higher values than previously reported for rat and rabbit liver, from which two forms of metallothionein with pI values of 4.2 and 4.7 have been isolated (Cherian, 1974; Nordberg *et al.*, 1972). The possibility exists, though, that the single peak obtained in this study would have separated in two bands in a narrower pH gradient.

Metallothionein has been proposed to play an essential role in the detoxification of cadmium (Piscator, 1964). The present investigation demonstrates a protein component with low molecular weight. The separation characteristics of the protein, or possibly the protein complex of the lung cytosolic fraction are similar to

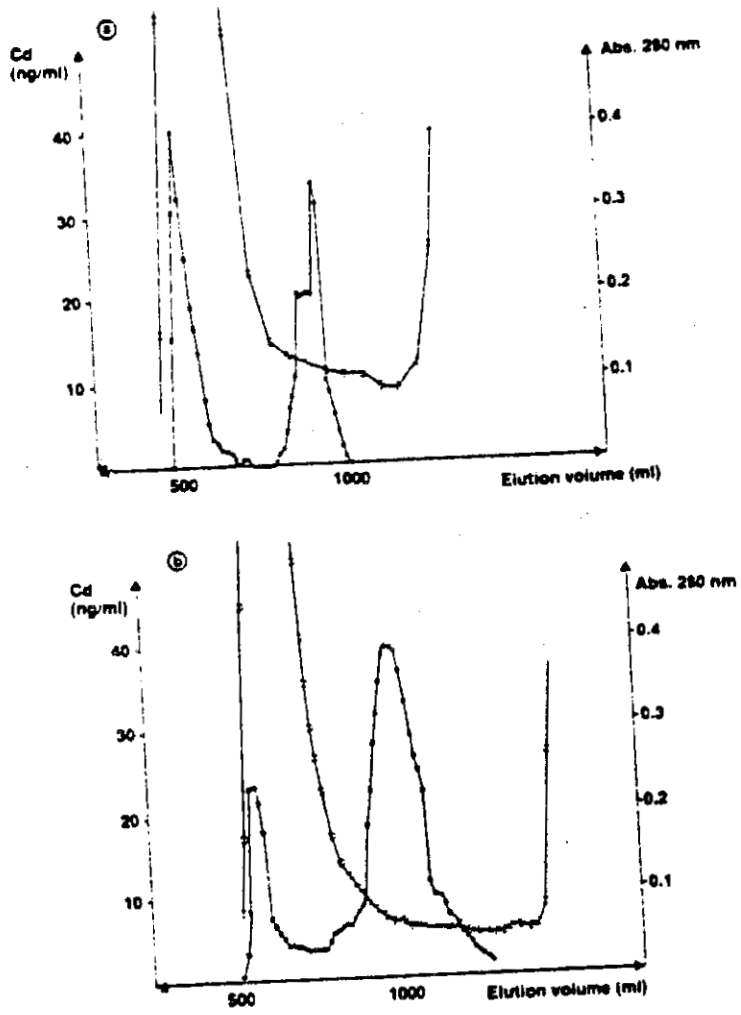


FIG. 1. Typical gel filtration chromatography in a 2.8 × 63-cm Sephadex column of tissue cytosolic fraction from one of the autopsied individuals (E.S.). (○) Denotes absorbance at 280 nm and (x), cadmium concentration in the fractions. (a) The elution pattern after application of 8.0 ml lung cytosolic fraction. (b) After 8.0 ml liver cytosolic fraction. (c) After 2.0 ml kidney cytosolic fraction.

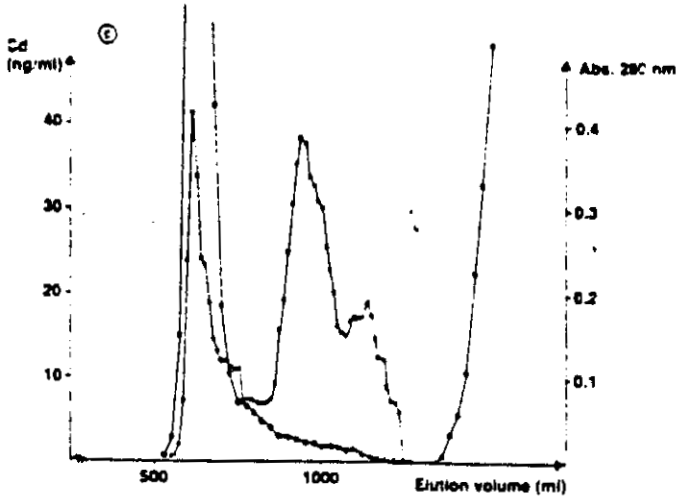


FIG. 1—*Continued*

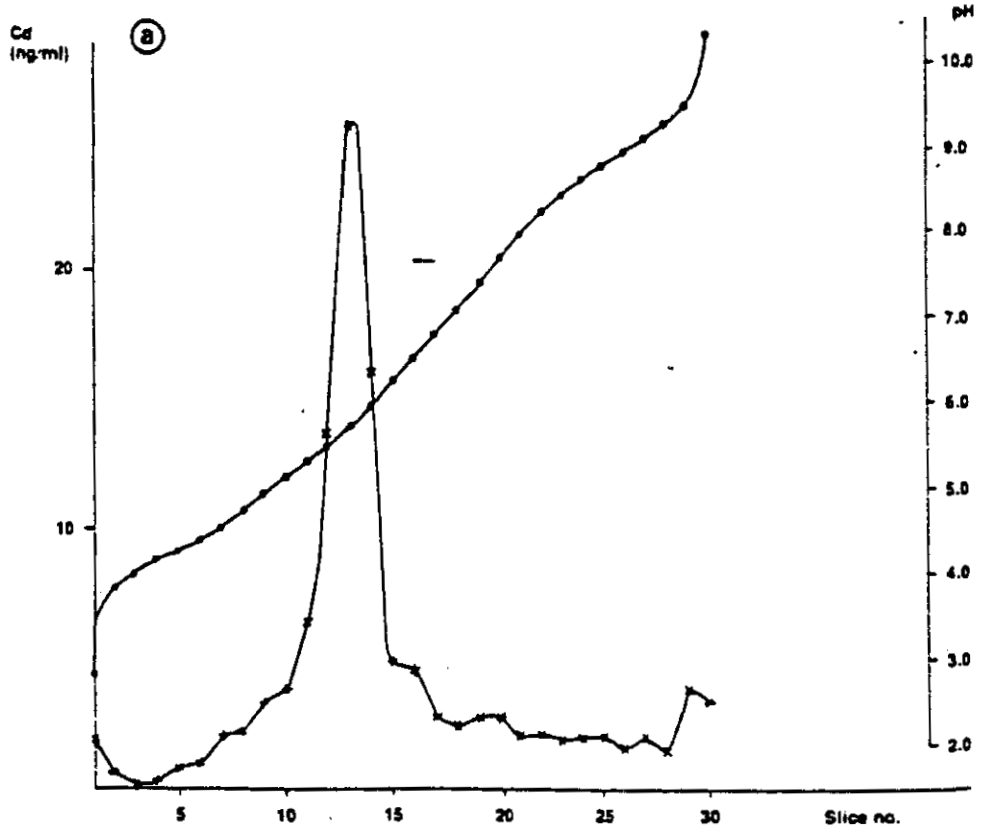
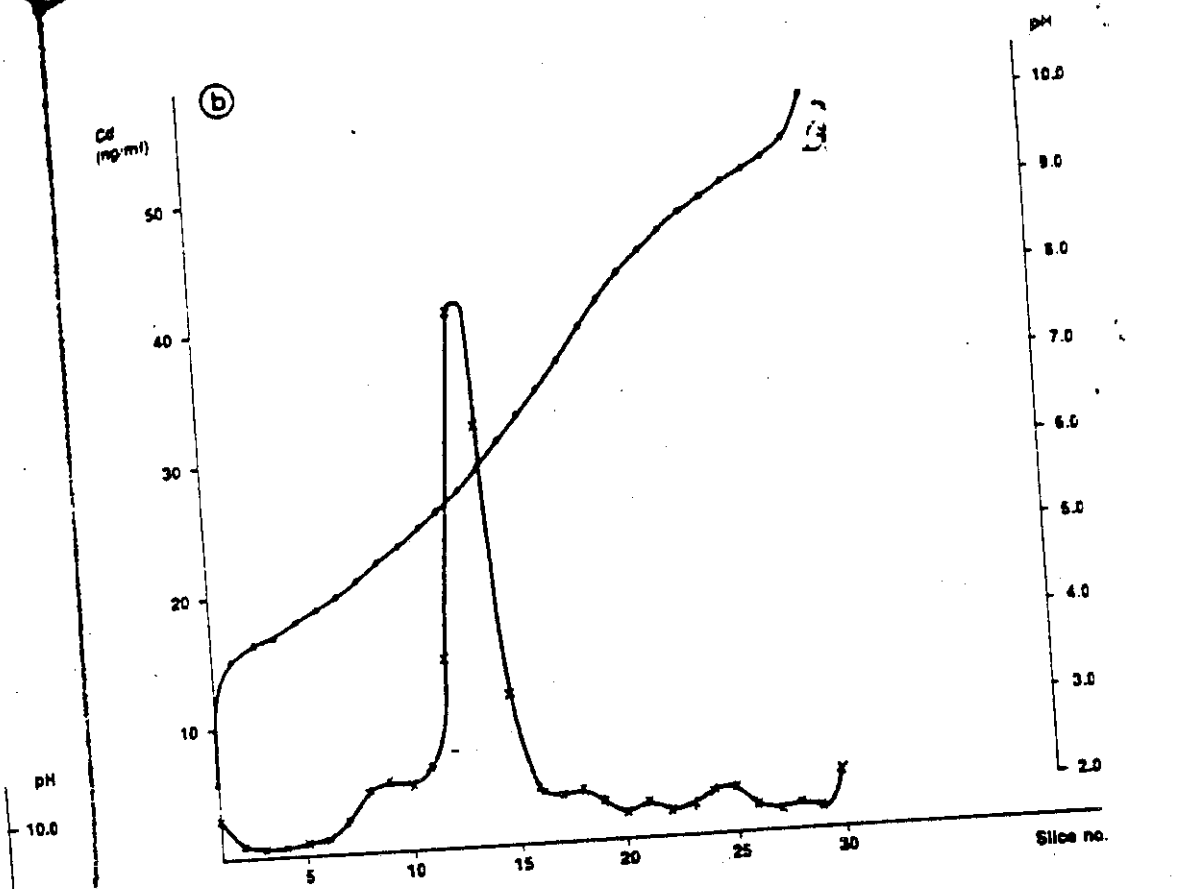


FIG. 2. Flat bed isoelectric focusing of 1.0 ml concentrated CdBP from all individuals pooled. (● Denotes pH gradient and (x), cadmium concentration in extracts of the gels. (a) 1.0 ml lung CdBP containing 0.11 μg cadmium. (b) 1.0 ml liver CdBP containing 0.28 μg cadmium. (c) 1.0 ml kidney CdBP containing 1.90 μg cadmium.



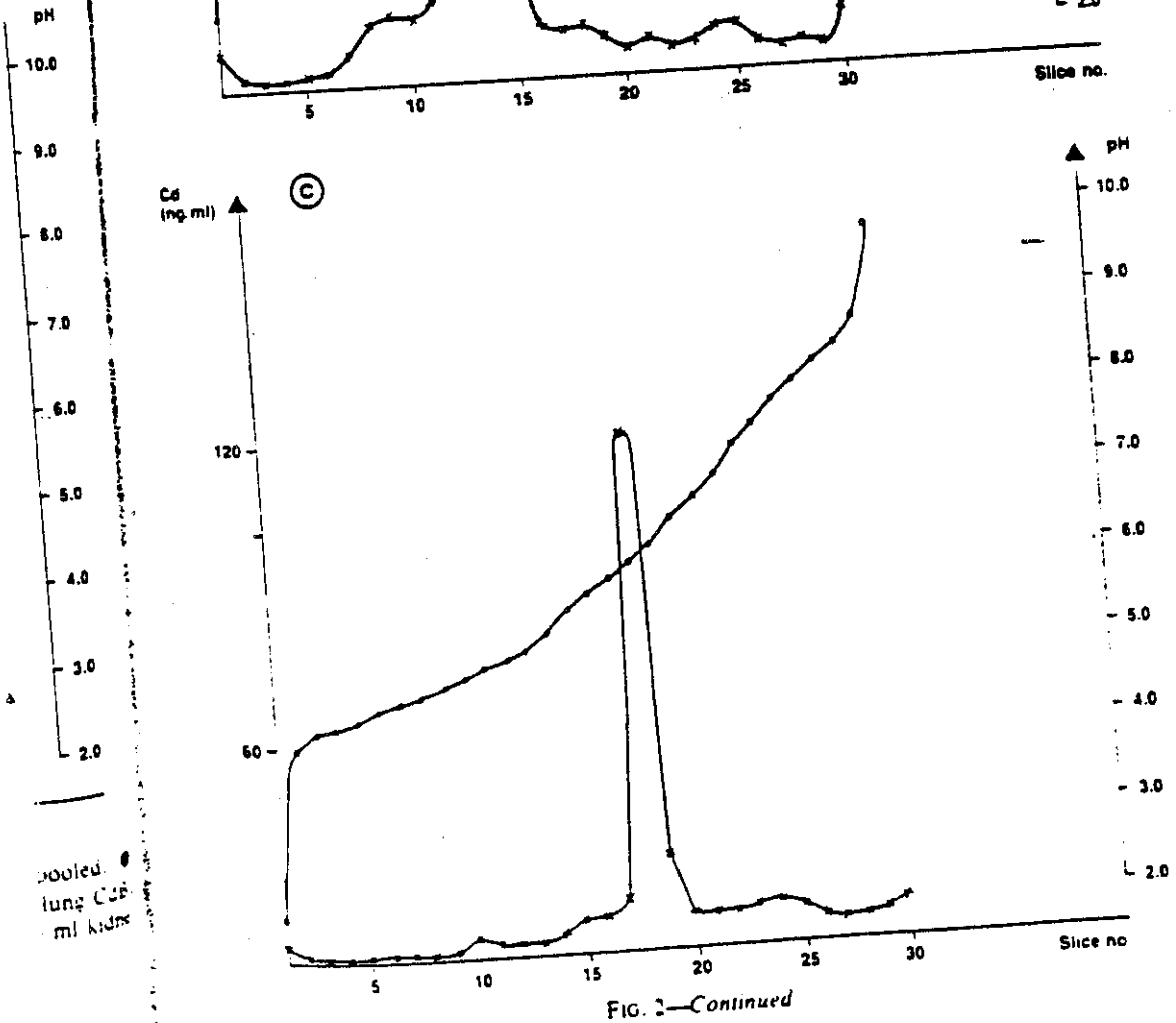


FIG. 2—*Continued*

that of liver or kidney. It is therefore likely that this protective factor against the toxic action of cadmium is present in human lung as well. It is interesting to note, however, that the cadmium-binding ability of lung tissue is less than that of liver or kidney tissue (Table 2). This could be an indication that the lungs are less capable to protect themselves against cadmium. A tempting speculation is therefore that individuals with subnormal capacity to synthesize the metallothionein-like protein are more susceptible to the toxic action of cadmium. A recently published study on the production of low-molecular-weight cadmium-binding proteins in the rabbit lung has shown this to be a rapid process, and that all cadmium is bound to the proteins within a few hours (Post *et al.*, 1982). The material taken postmortem in man was from old males, however, who had been exposed to large quantities of cigarette smoke. It is therefore not certain that their capacity to resynthesize the CdBP is sufficient. Another interesting aspect of this and other studies showing a lung CdBP, is that this CdBP could serve as a means of transporting the metal directly to the kidneys as has been indicated by others (Nordberg and Goyer, 1975; Johnson and Foulkes, 1980). Different capabilities to induce the protein could therefore give different body distribution of cadmium after deposition in the air passage.

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PACIFIC GAS AND ELECTRIC COMPANY

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August 20, 1986

Mr. William V. Loscutoff
Chief, Toxic Pollutants Branch
Air Resources Board
P.O. Box 2815
Sacramento, CA 95812

Dear Mr. Loscutoff:

Comments on Cadmium Risk Assessment

Pacific Gas and Electric Company appreciates this opportunity to comment on the Air Resources Board (ARB)/Department of Health Services (DHS) June 1986 Cadmium risk assessment.

We recommend that the DHS' Part B risk assessment be revised to:

1. state that the data are consistent with a threshold below which there is no risk from exposure, and that the range of risk is zero to 12 cases per million persons exposed to 1 ng/m^3 over their lifetime;

2. more clearly acknowledge that the unit risk recommendation is based upon the staff's no-threshold policy rather than any scientifically conclusive determination; and

3. recommend the use of the DHS' "best" risk estimate rather than the use of the DHS' "upper bound" risk estimate.

We recommend that the ARB's Part A source assessment be revised to:

4. address ship, railroad, and airplane cadmium emissions which a California Energy Commission (CEC) staff report indicates may be about nine times higher than the corresponding stationary source emissions;

5. clarify in Tables III and III-1, and in the text on page III-6, that one category, industrial boilers, contributes 70 percent of the total residual fuel oil combustion emissions and 60 percent of the total oil combustion emissions identified; and

6. explain why the ARB estimate of industrial boiler residual fuel use is three times higher than the corresponding CEC staff estimate.

We cannot overemphasize the importance of revising Part B to include a scientifically objective presentation of the cadmium threshold alternative. As discussed more fully in Attachment A, we urge DHS to estimate the threshold below which there may be no risk, and to use this threshold alternative in their range of risk estimate. Attachment B contains excepts from the 1985 Environmental Protection Agency (EPA) Cadmium Update which illustrates how such a threshold model comparison could be more objectively presented. We also note that Southern California Edison raised this issue in their January 21, 1985 comments (see ARB Report, Part C, SCE, page 6, bottom paragraph).

We disagree with the DHS recommendation that the upper bound risk estimate, rather than DHS' own "best" risk estimate, be used to estimate risks. DHS' reasoning that the upper bound risk is more appropriate because it provides an extra safety factor to protect "sensitive" populations and to protect against risk of death from cancer at other sites has not been scientifically justified. No data are cited indicating the existence of more sensitive populations. Also, there are no data that indicate increased risks of deaths from cancer at other sites (see revisions to Part B, page 63). Please note that EPA concluded that the use of the upper bound risk would be "an unnecessary added level of conservatism" (see EPA, page 163 in Attachment B).

Our comments on Part A are detailed in Attachment C. The applicable portion of the CEC Report referenced is attached as Attachment D. Please call me at (415) 972-6901 or J. T. Holcombe at (415) 972-6910 if you have any questions about these comments.

Sincerely,

Attachments

ATTACHMENT A

PART B OF THE JUNE 1986 CADMIUM RISK ASSESSMENT SHOULD BE REVISED TO STATE THAT THERE MAY BE A THRESHOLD BELOW WHICH THERE IS NO RISK FROM EXPOSURE, AND THAT THE RANGE OF RISK IS ZERO TO 12 CASES PER MILLION PERSONS EXPOSED TO 1 ng/m^3

In its 1985 Cadmium Risk Assessment Update the United States Environmental Protection Agency (EPA) properly addressed the likelihood that there could be a threshold for cancer risks from cadmium exposures. EPA concluded that its simple threshold model adequately fit the data.[1] EPA further concluded that:

1. There is no solid scientific basis for any mathematical model that relates carcinogen exposure to cancer risks at the extremely low concentrations that must be dealt with in evaluating environmental hazards;[2] and

2. An empirical threshold model that is also consistent with the observed data gives a unit risk estimate of zero[3] at typical ambient exposures.

In California, the Department of Health Services (DHS) is required to estimate "the range of risk to humans resulting from current or anticipated exposure".[4] We believe that refers to the full range of risk, which in this case should be stated as zero to 12 cases per million persons exposed to 1 ng/m^3 of cadmium. Although the DHS qualifies its estimate of 2-12 cases per million by stating that "the actual risk may lie in or below that range"[5], this is not sufficient since other experts have acknowledged that a zero risk estimate could be equally valid. Specifically, EPA has estimated that a constant lifetime exposure to 10 $\mu g/m^3$ cadmium would not cause any risk under the threshold

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1 Updated Mutagenicity and Carcinogenicity Assessment of Cadmium, EPA-600/8-83-02 5F, June 1985 (final), page 159 attached.

2 EPA, page 138 attached.

3 EPA, page 8 attached.

4 Health and Safety Code Section 39660(c).

5 DHS Revisions to Part B, "Report to the Air Resources Board on Cadmium Submitted to the SRP for Review, page 4a.

model.[6] Since the highest average ambient concentration reported in the Part A Report was only 10.8 ng/m^3, the reported concentrations are a factor of one thousand below this plausible threshold, and a zero risk estimate is far more likely -- particularly since there is relatively little evidence that cadmium is particularly mutagenic even at high concentrations.

DHS seems to assert that since "the carcinogenic activity of cadmium may occur through a mechanism for which no threshold exposure level exists"[7] (emphasis added), there is no need to present an objective evaluation of the likelihood that it may not occur through such a mechanism. DHS should clearly acknowledge that there is no data establishing that threshold mechanisms could not predominate, and follow EPA's example and present an alternative threshold model which would best fit the data. DHS Tables I-7[8] and IX-6[9] should be expanded to include comparative risks at ambient concentrations under the alternate threshold assumption in a manner similar to that presented in EPA Table 26.[6] Similar comparisons should be included in DHS Table IX-2[10,11], Figure IX-1[12] and Figure I-1[13]. For clarity, the least squares fit data[14] should be tabulated in a manner similar to that shown in EPA Table 25[15]. Similarly, the DHS should follow the EPA Table 25 example on observed versus predicted data comparison by revising DHS Table IX-4[16] to also include a comparison with the incidence that would be predicted by the threshold model, not just with the incidence predicted by the linear no threshold model.

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6 EPA page 162 attached.

7 DHS Revisions to Part B, page 47.

8 DHS Revisions to Part B, page 6.

9 DHS Revisions to Part B, page 65.

10 DHS Part B (with revisions), page 84.

11 DHS Revisions to Part B, page 66.

12 DHS Part B (with revisions), page 85.

13 DHS Revisions to Part B, page 7.

14 DHS Revisions to Part B, page 62.

15 EPA, page 160 attached.

16 DHS Revisions to Part B, page 59.

If the DHS staff recommends a linear non-threshold upper bound range of risk estimate, any such recommendation should be clearly identified as being based on policy, not on a scientific determination. Furthermore, any such recommendations should only be made after DHS has objectively presented the full range of plausible alternative risk estimates -- including the EPA threshold model risk estimate. Risk managers need to know the relative likelihood of such a zero risk alternative so that they can consider the relative uncertainty of different upper bound risk assessments when faced with competing risk management alternatives.

ATTACHMENT B

EPA-600/8-83-025F
June 1985
Final

UPDATED MUTAGENICITY AND CARCINOGENICITY ASSESSMENT OF CADMIUM

Addendum to the Health Assessment Document for Cadmium
(May 1981) EPA-600/8-81-023

Office of Health and Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Washington, D.C.

Quantitative Assessment

Since humans are exposed to cadmium dust or fumes, and the rats used for study were exposed to cadmium chloride aerosol, a limitation inherent in the use of such studies for estimating human risk is the possible difference between humans and rats with regard to lung retention of particulates, or between the biological effectiveness of cadmium chloride aerosol administered to rats and the dust and fumes inhaled by workers. Since the data are not clear on this point, assumptions of equal lung uptake and equal effectiveness have been made herein for the purpose of arriving at an assessment of the human risks.

Given these assumptions, combined with other assumptions and conventions used in quantitative risk assessment procedures, the Takenaka et al. (1983) data on lung carcinomas in rats during lifetime inhalation exposures to cadmium chloride aerosol were analyzed. As a result of this analysis, the upper-bound incremental cancer risk to humans who continuously breathe 1 $\mu g/m^3$ of elemental cadmium for a lifetime is estimated to be 9.2×10^{-2}.

Based on respiratory cancer rates from the Thun et al. (1985) study of cadmium smelter workers, and using a linear model that is consistent with the data, the upper-bound incremental cancer risk from lifetime exposure to 1 $\mu g/m^3$ of cadmium in the air is estimated to be 1.8×10^{-3}.

The 95% confidence bound on this estimate, which takes into account only the statistical variability of the cancer rates, gives a range of 3.5×10^{-3} to 1.7×10^{-4}. However, this range does not account for possible deviations of the true (unknown) model from the linear model or of actual exposure from estimated exposure. For example, an empirical threshold model that is also consistent with the observed data gives a unit risk estimate of zero. Even with the uncertainties surrounding the estimate based on human data, it is felt that this

QUANTITATIVE ESTIMATION

INTRODUCTION

This quantitative section deals with the unit risk for cadmium in air and the potency of cadmium relative to other carcinogens that the Carcinogen Assessment Group (CAG) has evaluated. The unit risk estimate for an air pollutant is defined as the incremental lifetime cancer risk occurring in a hypothetical population in which all individuals are exposed continuously from birth throughout their lifetimes to a concentration of 1 $\mu g/m^3$ of the agent in the air that they breathe. These calculations are done to estimate, in quantitative terms, the impact of the agent as a carcinogen. Unit risk estimates are used for two purposes: 1) to compare the carcinogenic potencies of several agents with each other, and 2) to give a crude indication of the population risk that would be associated with air or water exposure to these agents, if the actual exposures were known.

The data used for quantitative estimation are taken from one or both of the following: 1) lifetime animal studies, and 2) human studies where excess cancer risk has been associated with exposure to the agent. In animal studies it is assumed, unless evidence exists to the contrary, that if a carcinogenic response occurs at the dose levels used in the study, then response will also occur at all lower doses with an incidence determined by the extrapolation model.

<u>There is no solid scientific basis for any mathematical extrapolation model that relates carcinogen exposure to cancer risks at the extremely low concentrations that must be dealt with in evaluating environmental hazards.</u> For practical reasons, such low levels of risk cannot be measured directly either by animal experiments or by epidemiologic studies. We must, therefore,

An estimate of $\Delta^* = \Delta \times 10^6$ is obtained from the equation

$$10.99 = \frac{2.35}{3.77 + 1.18\,\Delta^*} + \frac{29.63}{4.61 + 4.23\,\Delta^*} + \frac{39.09}{2.50 + 5.58\,\Delta^*}$$

which has the solution $\Delta^* = 0.642$ so that $\Delta = 6.42 \times 10^{-7}$. The $V(\Delta)$ is estimated to be $V(\Delta) = 1.27 \times 10^{-13}$ so that $\sqrt{V(\Delta)} = 3.56 \times 10^{-7}$, and the 95% upper and 5% lower confidence bounds are approximately $\Delta_u = 12.26 \times 10^{-7}$ and $\Delta_\ell = 0.58 \times 10^{-7}$, respectively. It should be noted that this measure of variability only takes into account random sampling error. It does not account for potential error due to an assumed incorrect model or biased exposure estimates.

To show how a different assumed model could influence risk estimates, the following ad-hoc "threshold" model can be considered. This model is not based on any biological information. It simply uses the highest dose group with no observable statistically elevated risk as the threshold and assumes linearity in accumulated dose beyond that point. It is assumed that

$$h(t) = \begin{cases} 0 & X < 1754 \\ \Delta\,(X - 1754) & 1754 < X \end{cases}$$

where 1754, the guessed-at threshold, is the boundary point of the maximum exposed group in $\mu g/m^3$-years. For this model an estimate of Δ is

$$\Delta = (7 - 2.5) \div (2522 - 1754) \times 2214 = 2.65 \times 10^{-6}$$

In Table 25 the fit of each model is shown and evaluated using the X^2 goodness-of-fit test.

We note that <u>both the "threshold" and linear models give an adequate fit to the data.</u> As a result, arguments other than purely statistical must be used to select the appropriate model.

TABLE 25. GOODNESS-OF-FIT MODELS FITTED TO THE THUN DATA

Exposure interval $\mu g/m^3$-years midpoint	Number of cases expected under linear model using as the estimate of parameter Δ the			Expected number of cases under threshold model $\Delta = 2.65 \times 10^{-6}$ if $X > 1754$ $\Delta = 0$ if $X < 1754$	Observed
	Lower bound	MLE	Upper bound		
< 350 (168)	3.84	4.53	5.21	3.77	2
351-1754 (727)	4.85	7.33	9.80	4.61	7
> 1754 (2522)	2.82	6.08	9.34	7.00	7
	X^2 goodness-of-fit statistic				
	7.971	1.567	3.364	2.070	

SOURCE: Thun, letter of April 10, 1984; Thun et al., 1985.

TABLE 26. ESTIMATED RISKS FOR VARIOUS MODELS BASED ON THUN DATA

Model used	Risk due to a constant lifetime exposure of 1 $\mu g/m^3$	10 $\mu g/m^3$	100 $\mu g/m^3$
Linear nonthreshold			
Upper bound	3.5×10^{-3}	3.4×10^{-2}	2.9×10^{-1}
MLE	1.8×10^{-3}	1.8×10^{-2}	1.7×10^{-1}
Lower bound	1.7×10^{-4}	1.7×10^{-3}	1.6×10^{-2}
Threshold model	0.0	0.0	3.7×10^{-1}
April 1984 model[a]	1.9×10^{-3}	1.9×10^{-2}	1.7×10^{-1}

[a]Used in the External Review Draft of the Updated Mutagenicity and Carcinogenicity Assessment of Cadmium, prepared by the Office of Health and Environmental Assessment, U.S. Environmental Protection Agency, April 1984.

SOURCES: Thun, letter of April 10, 1984; Thun et al., 1985.

unit risk estimate of 1.8×10^{-3}. A higher estimate of 3.5×10^{-3} would be obtained if the 95% upper bound of the parameter were used. However, it is felt that this is an unnecessary added level of conservatism, since the model used already inflates the risk estimate if nonlinear components exist or confounding factors are present.

The unit risk estimate based on the animal bioassay, 9.2×10^{-2}, also gives a higher estimate. However, species differences and cadmium form differences make an estimate from this source intrinsically less reliable than the one derived from the assumed human exposures. In addition, it must be kept in mind that these are upper-bound estimates. The true unit risk could range from this upper bound to a very small value approaching zero.

RELATIVE POTENCY

One of the uses of the concept of unit risk is to compare the relative potencies of carcinogens. For the purposes of the present analysis, potency is defined as the linear portion of the dose-response curve, and is used to calculate the required unit risk factors. In this section, the potency of cadmium is compared with that of other chemicals that the CAG has evaluated as suspect carcinogens. To estimate the relative potency on a per mole basis, the unit risk slope factor is multiplied by the molecular weight and the resulting number, expressed in terms of $(mmol/kg/day)^{-1}$, is called the relative potency index.

Figure 2 is a histogram representing the frequency distribution of relative potency indices for 54 chemicals that have been evaluated by the CAG as suspect carcinogens. The actual data summarized by the histogram are presented in Table 27. Where human data have been available for a compound, such data have been used to calculate these indices. Where no human data have been

ATTACHMENT C

PART A OF THE JUNE 1986 CADMIUM RISK ASSESSMENT SHOULD BE REVISED TO INCLUDE BUNKER C FUEL OIL USE BY SHIPS, AND TO DISTINGUISH BETWEEN INDUSTRIAL STEAM GENERATOR FUEL USE AND OTHER FUEL USE CATEGORIES

The California Energy Commission (CEC) March 14, 1986 staff draft Biennial Fuels Report lists in Table A-2, page A-4 of that report, fuel deliveries by category through 1984. Converting their data, expressed as trillion BTUs, into million gallons of oil[1] yields the following:

Fuel Oil Deliveries by End User Category	Residual Only 1983	Residual Only 1984	Residual and Other[2] 1983	Residual and Other[2] 1984
Electric Utility	439	148	439	148
Residential	0	0	0	0
Commercial	134	134	134	134
Industrial	309	309	4,610	4,939
Transportation	2,258	2,923	2,923	2,923

PGandE recommends that the utility fuel use in Appendix C of the ARB's Part A Cadmium Report be revised to reflect the 1984 data. That data, which indicates emissions decreased by a factor of 3, appears more representative of current fuel use projections.

PGandE notes that the ARB estimate of industrial boiler residual fuel use in Appendix C is roughly three times the corresponding CEC estimate for all industrial residual fuel oil deliveries. That difference should be explained. If it reflects the inclusion of oil field steam generator combustion of heavy crude, PGandE recommends that such heavy crude emissions be separately calculated and listed. The heavy crude generally used in such steam generators is likely to be far higher in sulfur and heavy metal content than the corresponding low sulfur residual fuels more typically used by other industries. Also, it is likely that such emissions will either substantially decrease if current oil prices prevail, or will be replaced by natural gas fueled cogeneration projects if oil prices return to previous highs.

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1 Assuming 42 gallons/6.25 million BTU.

2 "Other" is other than motor gasoline, distillate, and residual and presumably includes both crude combustion and feedstock use.

Given that the CEC identifies nine times as much residual fuel oil use in the ship and rail transportation sector as in the industrial sector, and the ARB identifies industrial boilers' use of residual fuel oil as the second largest source of cadmium emission in the state, the report should be revised to include ship and railroad use of Bunker C fuel oil. The report should also consider aviation fuel use, which the CEC estimated was 2,634 million gallons in 1984.

PGandE recommends that ARB Tables III (page 14) and III-1 (page III-5) be revised to more accurately reflect the data in Appendix C. As detailed in Appendix C, industrial boiler residual fuel use contributes more than 70 percent of total residual fuel emissions and more than 60 percent of total oil combustion emissions. Yet no mention of this appears in either table or in the descriptive paragraph on page III-6. PGandE recommends that Table III be revised to replace the oil, coal, and motor vehicle categories with the following: industrial steam generators; other stationary source fuel combustion; motor vehicle fuel combustion; and other mobile source fuel combustion. In Table III-1, the "industrial steam generator" category should be subdivided into its primary contributors, presumably low sulfur fuel oil boilers and high sulfur oil field steam generators. Similarly, the "other mobile source" category should be subdivided in Table III-1 into ship, rail, and aviation fuel related emissions. The other categories: utility residual fuel, commercial residual fuel, distillate fuel oil, coal, waste oil, and sludge incineration are comparatively insignificant. Nevertheless, we recommend also listing each such category in Table III-1 to give the public a better perspective of the relatively low levels of such emissions.

In 1984, PGandE sampled cadmium concentrations in ten fuel oil tanks at six different PGandE power plant sites. Concentrations in three tanks were below the initial detection limit of 0.5 ppm. Concentrations in the remaining eight tanks averaged 0.39 ppm, with none measured higher than 0.52 ppm or lower than 0.31 ppm. This data is consistent with the 0.38 ppm data previously submitted by Southern California Edison. PGandE therefore recommends that the ARB not continue to imply that concentrations ranging as high as 5.1 ppm would be equally likely.

Since utility emissions are insignificant even at 5.1 ppm, and since similar ranges are not calculated for industrial boiler residual fuel use where the variety of source emission controls and permissible sulfur content is far higher and suggestive of far greater variations in cadmium emissions, PGandE recommends that only the 0.38 ppm utility estimate be reflected in Table III and III-1.

ATTACHMENT D

Biennial Fuels Report

CALIFORNIA ENERGY COMMISSION

March 14, 1986

TABLE A-2

HISTORICAL
DELIVERIES BY SECTOR
(Trillions of Btu)

SECTOR/ENERGY TYPE	1976	1977	1978	1979	1980	1981	1982	1983	1984
Electric Utility									
Natural Gas(22)	302	364	312	458	534	678	571	486	599
Petroleum									
Distillate(24)	0	0	0	0	0	0	2	2	2
Residual(25)	596	774	619	640	391	284	99	65	22
Subtotal	596	774	619	640	391	284	101	67	24
Coal(26)	135	141	110	138	152	165	187	188	182
Hydropower(27)	210	109	237	191	264	253	384	448	451
Nuclear(11)	51	87	81	96	51	36	37	43	138
Geothermal and Other(12)	74	74	60	80	101	113	91	130	134
Total	1,368	1,549	1,419	1,603	1,493	1,529	1,371	1,362	1,528
Electricity Delivered(28)	520	527	545	567	566	591	578	584	611
Conversion Loss	800	976	821	983	870	893	764	704	797
Transmission Loss(29)	48	46	53	53	57	45	39	74	120
Total Loss	848	1,022	874	1,036	927	938	793	778	917
Residential End User									
Electricity(30)	154	162	174	182	176	183	179	187	200
Natural Gas(31)	610	569	584	621	557	518	559	515	502
Petroleum(35)									
Distillate Fuel Oil	5	7	7	7	1	1	1	1	1
Subtotal Petroleum	5	7	7	7	1	1	1	1	1
LPG(37)	9	9	14	18	18	16	16	15	15
Subtotal Residential	777	747	779	828	752	718	755	718	718
Commercial End User									
Electricity(30)	194	187	191	198	204	197	197	203	213
Natural Gas(31)	183	187	174	177	165	178	187	173	172
Petroleum(35)									
Motor Gasoline	11	13	16	14	10	8	8	8	8
Distillate Fuel Oil	9	13	13	10	21	30	29	27	27
Residual Fuel Oil	25	27	25	28	43	40	35	20	20
Subtotal Petroleum	45	53	54	52	74	78	72	55	55
LPG(37)	2	2	3	3	3	3	3	3	3
Subtotal Commercial	424	429	422	430	446	456	459	434	443
Industrial End User									
Electricity(30)	172	178	180	187	186	211	202	194	198
Natural Gas(31)	747	693	674	769	728	682	609	513	562
Petroleum(35)									
Motor Gasoline	8	6	5	6	9	7	7	7	7
Distillate Fuel Oil	78	104	110	138	105	112	127	103	103
Residual Fuel Oil	106	107	90	89	85	59	55	46	46
Other Petroleum	544	661	756	711	681	784	569	640	689
Subtotal Petroleum	736	778	961	944	880	962	758	796	845
LPG(37)	54	47	47	41	39	39	35	27	37
Coal(26)	57	66	60	60	69	72	65	26	26
Subtotal Industrial	1,766	1,762	1,922	2,001	1,902	1,966	1,669	1,556	1,658
Transportation End User									
Petroleum(35)									
Motor Gasoline	1,288	1,378	1,384	1,427	1,353	1,306	1,325	1,400	1,400
Aviation Fuels	336	372	387	381	363	348	335	357	392
Distillate Fuel Oil	211	257	280	249	259	281	252	331	356
Residual Fuel Oil	188	236	289	324	410	385	330	336	435
Lube Oil	1	1	1	2	2	3	3	3	2
Subtotal Petroleum	2,025	2,244	2,351	2,383	2,387	2,323	2,245	2,427	2,585
LPG(37)	1	1	1	2	2	3	3	3	3
Subtotal Transportation	2,026	2,245	2,352	2,385	2,389	2,326	2,248	2,430	2,588
Total End User	4,993	5,183	5,465	5,644	5,489	5,466	5,131	5,138	5,407

TOTAL END USER DELIVERIES

End User Deliveries									
Electricity	520	527	545	567	566	591	578	584	611
Natural Gas	1,840	1,449	1,432	1,567	1,460	1,378	1,365	1,201	1,226
Petroleum(34)									
Motor Gasoline	1,307	1,397	1,405	1,447	1,372	1,321	1,340	1,415	1,415
Aviation Fuels	336	372	387	381	363	348	335	357	392
Distillate Fuels	303	381	410	404	386	424	409	462	487
Residual Fuels	319	370	404	441	538	514	420	402	501
Misc. Fuels	545	563	757	713	683	757	572	643	691
Subtotal Petroleum	2,810	3,083	3,363	3,386	3,342	3,364	3,076	3,279	3,486
Liquified Petroleum Gas	66	58	65	64	62	61	57	48	58
Coal	57	66	60	60	69	72	65	26	26
Total End User	4,993	5,183	5,465	5,644	5,489	5,466	5,131	5,138	5,407

Western Oil and Gas Association
727 West Seventh Street, Los Angeles, California 90017
(213) 627-4866

August 19, 1986

Members of the Board
California Air Resources Board
1102 "Q" Street
Sacramento, CA. 95812

Subject: Comments of the Western Oil and Gas Association on Draft Report to the Air Resources Board on Cadmium

Dear Board Members:

Once again Western Oil and Gas Association (WOGA) appreciates the opportunity to comment on the risk assessment procedure as applied by the Air Resources Board (ARB) to control ambient air concentrations of hazardous materials in California. The thrust of the following comments is directed to the draft cadmium document. There is much to support in the work. However, the final range is too small to describe precisely the inherent uncertainties in the risk estimate. Further, the degree of uncertainty in the cadmium risk assessment is minimized by mathematical manipulation which may be unjustified (i.e., DHS recalculated animal data disregarding conversions for differences in metabolic rate). In addition, it appears to WOGA that the Department of Health Services (DHS) has not been consistent in its approach to utilizing available human data for risk assessment. In some cases (e.g., benzene) animal data were used when valid human data were available and in other instances (e.g., cadmium) the reverse is true.

In regard to the cadmium draft report, we wholeheartedly concur with the use of human over animal data. Our experience has consistently found the human experience to be more valuable in predicting actual human risk. As DHS states in the cadmium document, the possible roles of chance, bias, and/or confounding variables, in distorting the true dose response relationship in the occupational study, were likely to be small. The net direction of these potential errors was more likely to result in an overestimate of substance potency. Thus, we believe as does DHS that use of the epidemiologic data in quantitative risk assessment is appropriate.

Two assumptions lead to a confidence in the calculated risk for cadmium that may be unwarranted. Although we agree that a range of risk is proper, in the case of cadmium the upper bound risk expressed by DHS (2×10^{-6} to 12×10^{-6} per ng/m^3) is too small a range to be useful and could mislead the risk manager by assigning more confidence than perhaps should be given to the estimation. Many critical assumptions affect this range, e.g., the extrapolation model, exposure assumptions, chemical speciation. In view of the fact that EPA concluded a simple threshold model would adequately fit the data, zero would be appropriate for a lower range. Clearly, a broader range would more appropriately describe the breadth of uncertainty we all agree exists. Further, the recalculation of the animal data, disregarding conversions for metabolic rate, has given

figures which are very close to the upper bound risk predicted by the epidemiology. This congruence may be coincidental and DHS's use of this data to lend additional support to the risk predicted from the human data is inappropriate. Given the large number of viable assumptions, myriad possibilities could be supported with some manipulation of the data.

Our review of the draft risk assessment for cadmium has suggested inconsistencies in DHS's use of human epidemiology for risk assessment. In contrast to the approach taken for cadmium, the benzene risk assessment was calculated from animal data although human data was available. This was apparently justified by the fact that it is common practice to use the 95% confidence limit based on the most sensitive site and species. WOGA believes the cadmium approach applies equally to the benzene database. We do not believe that animal studies are more than a surrogate for adequate epidemiology. Thus, valid epidemiological studies are the best source of data, eliminating the inherent uncertainty in extrapolating from animals to humans. The inconsistency of the approaches is perplexing in that DHS argues first for utilization of animal data (benzene) and then for employment of human data (cadmium).

The upper bound risk for benzene was derived from data on the most sensitive site in animals, the preputial gland in mice, a site which has no human analogue. More appropriate data might have been the epidemiology which DHS used to derive the lower bound risk calculation. Again, as DHS concludes in the cadmium risk assessment, even the use of the epidemiology data is likely to result in an overestimation of risk.

To conclude, WOGA urges ARB and DHS to:

- Be consistent in the approach and assumptions which underlie risk assessment for each chemical considered;
- Use human over animal data when available;
- Communicate the uncertainty inherent in the estimation of risk; and
- Avoid statements which unjustifiably diminish the uncertainty as this is misleading to the risk manager and may cause misappropriation of limited resources.

Sincerely yours,

Robert Harrison
Vice President and
General Manager

RH:va
cc: Mr. Bill Loscutoff, ARB
Chief, Toxic Pollutants Branch

AIR RESOURCES BOARD STAFF RESPONSES TO PUBLIC COMMENTS ON THE JANUARY 1986 DRAFT REPORT

Comment: Southern California Edison (SCE) claims that, in deriving an emission factor for utility boilers burning fuel (residual) oil, the ARB took the average of the highest identified emission rate from the Taback Study and the estimate from the Krishnan Study which applies to utility boilers with an electrostatic precipitator (ESP) control device.

Response: The ARB emission factor for utility boilers was based on all five tests reported in the Taback Study. Staff noted that SCE did not list data from one of these tests (#24) in its analysis. Although California utility boilers are not equipped with ESPs, Taback et. al. concluded that the ESP is a better control device for utility boilers than fabric filters (baghouses) or scrubbers. Therefore, ARB staff believes the emission factor was reasonably derived, and represented the best estimate based on available data. Because ESPs are not used by California utilities, and other control devices are less efficient (according to Taback), staff believes that use of tests from ESP-equipped utility boilers would, if anything, understate cadmium emissions.

Comment: SCE points out that the cadmium content of crude and fuel (residual) oils varies widely, and therefore data which are most representative of California power plants should be used to estimate emissions. SCE states that the average measured cadmium concentrations in fuel oil at two SCE power plants is 0.1 ppm.

Response: ARB staff agree that there may be variation in trace element concentrations in fuel oils; to reflect this, ARB staff has revised the report to include a range of emissions. Data provided by SCE subsequent to the issuance of the draft Report on Cadmium (December 1985) indicates that concentrations below 0.01 ppm have been measured in fuel oils at SCE power plants. This information was used to develop a low emission factor of 8.3 10^{-8} lb Cd/gallon oil. A high emission factor of 5.1 10^{-6} lb Cd/gal oil was calculated from the Krishnan Study. Using these emission factors, emissions from utility boilers were estimated to range between 0.02 and 1.1 tons year. This range brackets emissions calculated from the 0.1 ppm average cadmium in fuel oil reported by SCE.

Comment: The Cadmium Council, Inc. argues that airborne exposure to cadmium is minimal, and that this is a reason not to list cadmium as a toxic air contaminant.

Response: Review of data on atmospheric cadmium concentrations in the State shows that the average population exposure ranges between 1 and 2.5 ng/m^3 (for 21 million people), with long-term exposure near three large sources predicted to be 40 ng/m^3 (for 57,000 people). Using DHS recommended dose-response values, the resulting excess lifetime cancer risk is from 2 to 30 per million for a large number of Californians, and a worst-case excess lifetime cancer risk is 80 to 480 per million for almost 60,000 people living close to sources.

Comment: CalMat Co. pointed out that our estimates of 1981 California cement production were high by a factor of 3.7.

Response: ARB acknowledges this error and has corrected it; data on California cement production for 1984 have been used in the revised report (Part A, p. III-6, and Appendix C to Part A, p. C-4).

Comment: CalMat Co. pointed out that approximately 1.6 tons of feed material to the rotary kiln are needed to produce one ton of clinker (not cement, as stated in the report).

Response: According to the Bureau of Mines of the United States Department of the Interior (1), "About 1.8 tons of raw material are required to manufacture 1 ton of finished cement; 1.7 tons are used to make clinker, and the remaining 0.1 ton is added during the clinker-grinding process." Two other references (2, 3) reported a ratio of 1.6 to 1.0 for raw material to cement. ARB staff were aware of the different ratios reported by these references and chose to use a conservative estimate of 1.6 tons of raw material to 1.0 ton of cement.

Comment: CalMat Co. suggested that cadmium emissions from cement manufacturing could be estimated using data on particulate matter emissions from the rotary kilns used to produce clinker. CalMat Co. based their estimate on:

1. statewide cement production of 7.88 million tons (1981);
2. clinker production (approximately 95% of cement production) of 7.72 million tons;

3. a ratio of 1.6 tons kiln feed material to ton of clinker produced, yielding an estimate of 12.4 million tons kiln feed;
4. the assumption that all rotary kilns in California are equipped with fabric filter baghouses or electrostatic precipitators meeting Federal (EPA) New Source Performance Standards of 0.3 lb. particle emissions from the kiln per ton of kiln feed, giving an estimate of 3.71 million tons of emitted particulate;
5. a mean concentration of 21 ppm (by weight) cadmium in baghouse catch dust, which was assumed to be representative of emitted particulate matter. On this basis, CalMat Co. estimated cadmium emissions from rotary kilns to be 0.039 ton/year.

Response: ARB staff agrees with CalMat Co. that cadmium emissions from cement manufacturing can be estimated using estimated particulate matter (PM) emissions. However, CalMat Co. appears to have considered only estimated PM emissions from rotary kilns and has excluded emissions from other parts of the overall cement manufacturing process. Attached is a copy of the flow diagram of the Portland cement manufacturing process from the "Compilation of Air Pollutant Emission Factors", Fourth Edition (3). As seen in the diagram, the cement manufacturing process includes 1) quarrying and crushing, 2) raw material storage, 3) grinding and blending, 4) finish grinding, and 5) packaging. These processes are also potential sources of PM emissions. Normally, the emissions from quarrying, crushing, and raw material storage are not controlled.

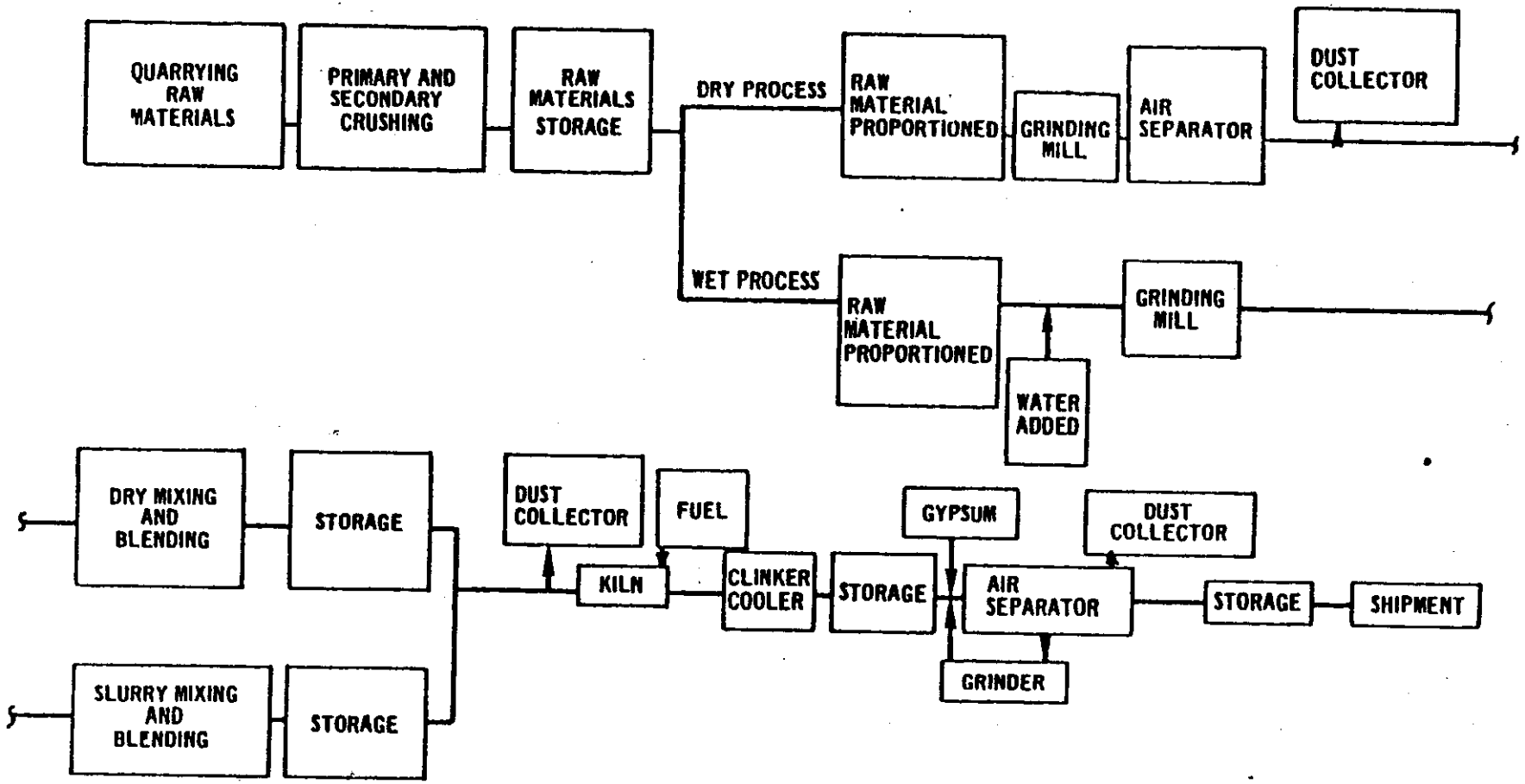

Figure 8.6-1. Basic flow diagram of portland cement manufacturing process.

In 1984, California cement manufacturing plants produced 8.72 million tons of cement (4) and emitted approximately 3,030 tons of PM (5) excluding PM emissions from fuel.

Assuming the cadmium concentration in the cement kiln dust removed from the rotary kiln baghouse or ESP equals the cadmium concentration in the particulate matter, cadmium emissions from cement manufacturing can be estimated from total PM emissions and the cadmium concentration in cement kiln dust.

The cadmium concentration in cement kiln dust from 9 California cement plants ranged from 5 ppm to 352 ppm and averaged 79 ppm (6,7). Using these data and the total PM emissions, the 1984 cadmium emissions from California cement plants are estimated to be:

Lower Estimate	Upper Estimate	Estimate based on mean Cd concentration
(TPY)	(TPY)	(TPY)
0.015	1.1	0.24

We have listed this range of 0.02 to 1.1 tons/year as cadmium emissions from cement manufacturing (see Overview, p. 14, Part A, p. III-5, and Appendix C, p. C-4).

Comment: PG&E recommends that the fuel use in Appendix C of the ARB's Part A Cadmium Report be revised to reflect 1984 data.

Response: 1984 data were not available at the time the original cadmium emission estimate for residual oil combustion was made. We have updated the estimate to reflect 1984 data.

Comment: "PG&E notes that the ARB estimate of industrial boiler residual fuel use in Appendix C is roughly three times the corresponding CEC estimate for all industrial residual fuel oil deliveries. That difference should be explained. If it reflects the inclusion of oil field steam generator combustion of heavy crude, PG&E recommends that such heavy crude emissions be separately calculated and listed. The heavy crude generally used in such steam generators is likely to be far higher in sulfur and heavy metal content than the corresponding low sulfur residual fuels more typically used by other industries. Also, it is likely that such emissions will either substantially decrease if current oil prices prevail, or will be replaced by natural gas fueled cogeneration projects if oil prices return to previous highs."

Response: Crude oil burned in boilers or steam generators at the oil fields may be included under residual fuel oil in the staff estimate. The emission data system (EDS) showed approximately 1.13 billion gallons of oil burned in the industrial category. Of this, aproximately 80 percent is burned for oil and gas production

activities (8). However, the data used did not differentiate between residual or crude oil. Therefore, we cannot separately estimate cadmium emission from residual or heavy crude oil combustion for this category. However, we agree with PG&E that heavy crude oil burned at oil field generators is higher in sulfur and metal content comparing to oil typically used by other industries. Thus, if crude oil is used, cadmium emissions from oil combustion may be underestimated.

There is uncertainty about future fuel use. We do not have an adequate basis to assume a substantial decrease in cadmium emissions from residual oil combustion for the industrial category as suggested by PG&E.

Comment: a) "Given that the CEC identifies nine times as much residual fuel oil use in the ship and rail transportation sector as in the industrial sector, and the ARB identifies industrial boilers' use of residual fuel oil as the second largest source of cadmium emission in the state, the report should be revised to include ship and railroad use of Bunker C fuel oil. b) The report should also consider aviation fuel use, which the CEC estimated was 2,634 million gallons in 1984."

Response: a) Even though CEC reports that the residual fuel oil used by the transportation sector is approximately nine times higher than that for the industrial sector (9), we have not been able to document the use of such a large amount of fuel use in California. We suspect that much of it is used by ships outside coastal waters.

Of the amount of residual fuel oil reported by CEC in the transportation sector, we have only been able to document about 2 percent in California (9,10). In the revised cadmium report, cadmium emissions will also be estimated for ships and trains under residual and diesel combustion categories, respectively. However, these emissions will not be separately listed.

b) We are aware of the fact that cadmium emissions would also result from aviation fuel combustion; however, we have no data to estimate cadmium emissions for this category.

Comment: "PG&E recommends that ARB Tables III (page 14) and III-1 (page III-5) be revised to more accurately reflect the data in Appendix C. As detailed in Appendix C, industrial boiler residual fuel use contributes more than 70 percent of total residual fuel emissions and more than 60 percent of total oil combustion emissions. Yet no mention of this appears in either table or in the descriptive paragraph on page III-6. PG&E recommends that Table III be revised to replace the oil, coal and motor vehicle categories with the following: industrial steam generators; other stationary source fuel combustion; motor vehicle fuel combustion; and other mobile source fuel combustion. In Table III-1, the "industrial steam generator" category should be subdivided into its primary contributors, presumably low sulfur fuel oil boilers and higher sulfur oil field steam generators. Simiarly, the "other mobile source" category should be subdivided in Table III-1 into ship, rail, and aviation fuel related emissions. The other

categories: utility residual fuel, commercial residual fuel, distillate fuel oil, coal, waste oil, and sludge incineration are comparatively insignificant. Nevertheless, we recommend also listing each such category in Table III-1 to give the public a better perspective of the relatively low levels of such emissions."

Response: Table III and III-1 of the cadmium report will be revised and the cadmium emissions from utilities will be mentioned. We do not believe it is necessary to greatly expand the detail in Table III-1 at this time as suggested by PG&E. Should airborne cadmium be listed as a toxic air contaminant, emission estimates for cadmium will be refined and detailed to support risk management activities.

Comment: a) "In 1984, PG&E sampled cadmium concentrations in ten fuel oil tanks at six different PG&E power plant sites. Concentrations in three tanks were below the initial detection limit of 0.5 ppm. Concentrations in the remaining eight tanks averaged 0.39 ppm, with none measured higher than 0.52 ppm or lower than 0.31 ppm. This data is consistent with the 0.38 ppm data previously submitted by Southern California Edison. b) PG&E therefore recommends that the ARB not continue to imply that concentrations ranging as high as 5.1 ppm would be equally likely."

Response: a) We appreciate PG&E providing information on the cadmium concentrations of residual oil used at its plants. These data will be considered in estimating cadmium emissions from residual oil combustion.

b) A factor of 5.1 ppm was not used to develop the high estimate for utility boilers. The factor used previously was 5.1 lbs Cd per million gallons of oil burned. New estimates based on a factor of 0.52 ppm have been developed.

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4. U.S. DOI, 1985. Mineral Industry Surveys, Cement in 1984. August 28, 1985. U.S. DOI, Bureau of Mines, Washington, DC.

5. California Air Resources Board (CARB), 1985a. Data retrieved from EDS, data base year 1984, on 3/5/1986. Emission Inventory Branch, Technical Support Division, Sacramento, CA.

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7. CARB, 1985b. Personal communication between Benjamin Haynes of U.S. DOI (Tel. (301) 436-7564) and Chris Nguyen of CARB on 2/28/86 regarding the identification of California cement kiln dust used in the "Characterization of U.S. Cement Kiln Dust" report.

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9. CEC, 1986. Biennial Fuels Report. Fossil Fuels Assessment Office, Assessments Division, California Energy Commission, Sacramento, CA.

10. CARB, 1986b. Data retrieved from EDS, inventory year 1983, run date 9-13-86. ARREPORT JOB 1954. Emission Inventory Branch, Technical Support Division, Sacramento, CA.

Department of Health Services

Staff Responses to Comments from the

Scientific Review Panel

(January 1986 Draft)

Comment:

The SRP stated that the DHS did not appear to have a policy for determining when to use animal data and when to use human data in a risk assessment.

Response:

The policy of the DHS staff has been to use the best evidence available for the risk assessment. The choice of human or animal data has been made on a case-by-case basis.

Human data are clearly preferable where studies are well designed and exposure is well documented, since this eliminates the uncertainty arising from interspecies extrapolation. Frequently, human exposure has not been well documented. In addition, information about potential confounding variables is often lacking.

On the other hand, in some cases the animal data may not be suitable. For example, in the animal data for asbestos, exposures were reported on mass basis instead of by fiber count. Since fiber count is the significant factor used in evaluating human health effects of asbestos, the DHS staff chose to use the human data.

Cadmium was the first chemical encountered in the AB 1807 process for which there was both a suitable animal study and a well designed human study with documented exposure estimates for individual workers and a positive

dose-response. This made it possible for the DHS staff to conduct two separate risk assessments.

Comment:

The SRP stated that DHS staff did not make clear the rationale for choosing to use the human-based risk assessment for cadmium.

Response:

As noted in the original report, the two risk assessments led to ranges of estimated risk that did not overlap. Using a more refined model to determine risk, the updated human-based assessment yielded a risk estimate about ten- to sixty-fold smaller than the animal-based assessment. In this instance, DHS staff chose to recommend the use of the human-based risk estimates even though these were smaller than the animal-based ones because:

(a) the use of a linear model with a correction for the healthy worker effect was judged to be sufficiently health-conservative,

(b) the amount of error in the measures of dose and effect from the Thun study were probably not large,

(c) the net direction of these errors was likely to result in an over-estimate of cadmium's carcinogenic potency.

To further clarify our reasons for adopting the human-based risk assessment we have expanded the description of the study by Thun et al. and the discussion of the potential roles of confounding, bias and chance in explaining the findings of this study. (Section VII.J.2 Human studies, Respiratory cancer-Thun study.)

Comment:

DHS staff found the evidence of carcinogenicity in humans to be sufficient, but did not state the grounds for this interpretation of the

evidence, nor the reasons why this conclusion differed from that of the IARC and the EPA.

Response:

Although the IARC has developed specific criteria for evaluating the evidence for human carcinogenicity as sufficient, limited or inadequate, the study by Thun et al. was not available to that agency when they last evaluated cadmium. Based on the evidence available at that time on prostate cancer, IARC (1982) concluded that there was limited evidence for carcinogenicity in humans. Based on the Thun study, the Environmental Protection Agency (EPA, 1985) also classified the evidence as limited. While they considered the Thun study to be very strong evidence of human carcinogenicity, the lack of another well-conducted study which confirmed these results influenced their decision not to classify the evidence as sufficient. For the purpose of risk assessment, it is unnecessary for the DHS to make such a judgment because cadmium is clearly an animal carcinogen. Since the IARC, the EPA and the DHS consider animal carcinogens to be potential human carcinogens, cadmium is a candidate for a quantitative risk assessment. The document has been revised to reflect this.

Comment:

The SRP questioned the recommendation of the DHS staff to use the human-based risk assessment when the EPA found the animal evidence adequate for use in risk assessment.

Response:

The DHS also found the animal evidence adequate for use in risk assessment. Both EPA and DHS performed two risk assessments, one based on animal data and one based on human data. EPA also chose to recommend their

human-based risk estimate rather than their animal-based estimate, stating "species differences and cadmium form differences make an estimate from this source (animal) intrinsically less reliable than the one derived from the assumed human exposures" (EPA, June 1985). Though their choice of model for the human-based risk estimation differed from the one used by the staff of DHS, the final estimates were quite close.

Comment:

The model used by the DHS for quantitative risk estimation may not have been the best choice, particularly since it did not accomodate all of the data.

Response:

DHS staff has revised the risk assessment by fitting a more appropriate model which accomodates all of the data. This model regresses the observed deaths as a function of two factors: the cumulative dose and the expected deaths. This function has two parameters: one for the carcinogenic potency of the cumulative dose, and the other for the observed "healthy worker effect." Since the low exposure group experienced a marked deficit of lung cancer deaths, these workers can be inferred to represent a healthier group than the general population of white males of the same ages. By estimating the degree to which the cohort under study differs from the population, this model separates the effect of dose from the countervailing healthy worker effect. In particular, it ensures a more health-conservative estimate of carcinogenic potency.

Comment:

The SRP wished to see the range for extrapolation between the observed data and the ambient levels in California.

Response:

The workers were exposed to cumulative doses which were equivalent to a constant 24-hour/day lifetime exposure of concentrations of 2.7, 11.8 and 41.0 $\mu g/m^3$. Ambient air in California is estimated to contain concentrations of 1 to 2.5 ng/m^3. Thus using the daily dose rate, the range of extrapolation is 10^{-3}, (three orders of magnitude) or a thousandfold. The median cumulative exposures for the workers were 184, 796 and 2762 mg-days/m^3 while the population in California would be expected to receive on average, over an 80-year lifespan, .029 to .073 mg-days/m^3 . (1 ng X 365 days X 80 years = 29200 ng-days/m^3 = .029 mg-days/m^3.) Thus using lifetime cumulative dose, the range of extrapolation is 3-4 orders of magnitude. In some hot spots, California residents would be expected to receive 1.17 mg-days/m^3 representing exposures 2 - 3 orders of magnitude lower than the workers' exposures. The range of extrapolation has been included in the revised Executive Summary of Part B of the document.

Department of Health Services

Staff Responses to Public Comments

(January 1986 Draft)

Comment:

Ciba-Geigy objected to the use of occupational exposures for extrapolating risks at ambient levels of cadmium, which are several orders of magnitude lower. They argued that (a) cadmium levels declined over time, (b) workers were also exposed to arsenic, lead and zinc, (c) urine levels indicated high exposures, which may have been the result of poor hygiene practices, (d) "smoking could have accounted for half the increase," and (e) smoking habits were determined retrospectively.

Response:

The uncertainty involved in extrapolating to very low ambient levels is acknowledged by DHS staff. However, it is not feasible to directly observe the carcinogenic effect of low-level chemical exposures. The only quantitative data on cadmium's carcinogenicity are (1) experimental animal data involving daily exposures close to the OSHA permissable exposure level, and (2) the occupational study by Thun et al.

The decline in cadmium levels over time was reflected in the exposure assessment carried out by Thun et al. The effect of arsenic was evaluated by Thun et al., and is discussed in the revised Section VII.J.2 Human studies, Respiratory cancer: Thun study. The hygiene practices of the cohort are not an issue since the risk assessment was based on air monitoring data, and the hygiene practices are irrelevant to lung exposures. Issues related to smoking have been reviewed (see revisions in VII.J.2 Human studies, Respiratory cancer: Thun study).

Comment:

Ciba-Geigy argued that studies of environmental cadmium exposures did not detect adverse health effects.

Response:

The study by Lauwerys (1984) was not concerned with carcinogenicity, but with body burdens of cadmium in relation to nephrotoxicity. With regard to data from Japan, the commentor provided no references.

Comment:

Southern California Edison criticized the ad hoc model which DHS used in its risk assessment, and in particular, the exclusion of data which did not fit the model.

Response:

DHS staff has repeated the risk assessment using a different model which accommodates all the data. (See revised Section IX.B.2)

Comment:

Southern California Edison pointed out that DHS staff incorrectly assumed that the exposures reported by Thun et al. were quantified in units of CdO (cadmium oxide).

Response:

DHS staff acknowledges this error and has corrected it.

Comment:

Southern California Edison questioned the background rate for lung cancer used by DHS on the grounds that it was higher than the rate used by EPA.

Response:

DHS staff has employed 1979-80 California age-specific rates for lung cancer as the background level. The cumulative lifetime probability of

dying of lung cancer by age 80 in California is .055 for males and .025 for females. (See Appendix D in the revised document.)

Comment:

Southern California Edison objected to the use of a nonthreshold model, citing the lack of elevated cancer risk in the lowest exposure group of the study by Thun et al.

Response:

The use of a nonthreshold model is based on theoretical, biological considerations. The staff of DHS does not consider occupational epidemiological studies to be adequate for evaluating whether a threshold process is responsible for inducing cancer. Occupational mortality studies have no ability to distinguish mechanisms by which an effect is induced. The threshold issue is discussed with regard to the mechanisms specific for cadmium-induced carcinogenicity in revised Section VIII. With regard to the data of Thun et al., the lack of response in the low exposure group can be explained as a manifestation of the healthy worker effect, which was also observed for cardiovascular deaths.

Comment:

Southern California Edison argued that the evidence for human carcinogenicity is not sufficient and that the position of DHS was not justified.

Response:

DHS staff has revised the document and has determined that such a judgement was unnecessary because there is sufficient evidence to consider cadmium an animal carcinogen and therefore a potential human carcinogen. (Refer to revised Section VII.J.4 CANCER: Conclusion and to DHS staff responses to SRP comments.)

Comment:

Southern California Edison pointed out that the combined effects of smoking and arsenic may be greater than the sum of the two.

Response:

DHS staff acknowledges that confounding by either of these two risk factors and by their interaction could explain some of the excess lung cancer deaths. Because of the low levels of arsenic and the data indicating a deficit of smokers in the cohort, those two factors are unlikely to account for all of the excess, even assuming a multiplicative effect of arsenic and smoking. (A full discussion is in the revised Section VII.J.2, Human studies, Respiratory cancer-Thun study. Also, see Tables VII-11 to VII-14, especially VII-14.)

Comment:

Southern California Edison argued that the DHS should refrain from recommending upper bound risk estimates until results are available from the nested case/control study being conducted by Thun et al., and until uncertainties in this study have been resolved.

Response:

The DHS is mandated to provide a quantitative risk assessment under California Health and Safety Code 39660. We have attempted to utilize all of the most recent available data in our evaluations and estimates of risk, including the presentations by Dr. Lamm and Dr. Thun at the Fifth International Cadmium Conference. In the revised risk assessment, DHS staff has attempted to clarify areas of uncertainty arising from the data.

Comment:

The Cadmium Council, Inc., argued that the evidence of human carcinogenicity is inadequate and that the critical epidemiological study by Thun et al. is still being reanalyzed. They cited several critisims of this

study: (a) individual estimates of arsenic exposure were not obtained, (b) potential interactive effects of arsenic and smoking were not evaluated. They also submitted several unpublished documents including a manuscript by Dr. George Kazantzis describing a further follow-up of an earlier study of a cohort of workers potentially exposed to cadmium, and a nested case/control study of lung cancer deaths in the cohort.

Response:

The weakness in not having individual arsenic exposure estimates is a concern, but the cohort calculations of Thun et al. indicate that the contribution of arsenic to the excess lung cancer death rate was not large. Evidence presented in the update of this study indicate that arsenic levels have been quite low since 1926, in contrast to the assertions of Dr. Lamm. The issue of interaction is discussed in our revised document. Given the deficit of smokers in the cohort relative to the general population and the low overall risk from arsenic, the interaction of smoking and arsenic exposure is likely to have made a negligible contribution to the excess cancer mortality. This is because at low relative risks, a multiplicative effect is only negligibly different from an additive effect. The case/control study conducted by Kazantzis purports to show no association between cadmium exposure and lung cancer mortality. Although the report contains numerous inconsistencies and is therefore difficult to follow, it appears that the (nonstatistically significant) estimate of relative risk associated with a decade of exposure to 1 $\mu g/m^3$ cadmium was almost identical to the (statistically significant) relative risk associated with a "decade level" of arsenic exposure, with arsenic exposure classified on a scale of 0 to 2. Rather than being strong evidence of no effect, these data show weak evidence of an effect. Furthermore, the exposures of these workers were

much lower than those in the study by Thun et al. Only 21 workers received exposures that were anywhere near as large as the median of the low exposure group in the Thun study. As Kazantzis states, "The present results are not inconsistent therefore with Thun's, but there is very little power to detect a cadmium effect."

Comment:

The Cadmium Council, Inc., objected to the statement by DHS that we "do not believe there is evidence to reject an effect of cadmium on prostatic cancer." They asserted that the statistical evidence is convincing that no effect exists.

Response:

The DHS disagrees that a conclusion of no effect is justified. The reasons were presented in the original document (pp. 66-68 of part B): (1) the highly significant early reports, (2) the persistence of small (nonstatistically significant) elevated risks in recent studies, (3) the decline in level of industrial exposure, and (4) the low statistical power of these studies. In total, DHS staff regards the evidence as inconclusive. For clarification, the sentence referred to by the Cadmium Council, Inc., has been changed to state "the staff of DHS does not believe that the evidence is conclusive to reject an effect of cadmium on prostate cancer."

Comment:

The Cadmium Council, Inc., stated that although EPA's Science Advisory Board (SAB) found the Takenaka study to be sufficient evidence of cadmium's ability to cause cancer in animals, the SAB felt that more information was needed on the actual particle size distribution of ambient cadmium to which the general public would be exposed. This information would allow a comparison for the purpose of quantitative risk assessment, of the effective dose given to the rats in the Takenaka study with typical human exposure.

Response:

The ARB did not estimate the distribution of particle size in ambient California air. However, since the animal study was not used for final risk estimates, it is not really necessary for a comparison of effective dose. If such a comparison were made, it is likely that a modification in ambient exposure could be made that would reflect a lower exposure to cadmium because some ambient particles containing cadmium would not be respirable. In our assessment with occupational exposure, it was assumed that the particle size distribution in the occupational setting and in ambient air were similar. The validity of this assumption cannot be verified.

Comment:

The Cadmium Council, Inc., asserted that the effect of solubility on the bioavailability of various cadmium compounds would be likely to result in a difference in their toxic potency. The ARB draft document indicated that absorption may not be dependent on solubility, citing a study which compared the pharmacokinetics of cadmium chloride and cadmium oxide in the lung. Information on cadmium red and yellow pigments suggests that solubility is important.

Response:

The statement in the ARB document has been changed to explicitly pertain only to cadmium chloride and cadmium oxide. It is important to note that the ARB has concluded that cadmium oxide, cadmium carbonate, and cadmium sulfate are the likely principal constituents of ambient airborne cadmium. Cadmium sulfate is soluble, while the oxide, which is relatively insoluble, appears to act in the lung like cadmium chloride, a soluble salt. It is not known how cadmium carbonate acts in the lung. However, in an unpublished paper by Rusch et al. that was supplied by commentors, cadmium carbonate appeared to be much more soluble and more toxic than cadmium red

or yellow pigments following inhalation. Since there has been no speciation of ambient airborne cadmium DHS staff has assumed that all inhaled cadmium will act as if it were soluble.

Comment:

Ciba-Geigy argued that since cadmium chloride increases both epithelial permeability and the number of inflammatory cells in the lung, the continual presence of this chemical in the lung without any possibility for lung clearance and repair was probably responsible for the increased tumor incidence observed in the study by Takenaka et al.

Response:

Although nontumor pathology was not reported in great detail in the Takenaka study, there is little reason to believe that there had been significant pulmonary lesions as suggested by the commenter. A dose-related increase in lung fibrosis was found in the treated animals of the Takenaka study, but the severity of the lesions and any relationship they have with the observed tumors is unknown (personal communication with Gunter Oberdorster, 2/18/86). Lung damage was likely to have been minimal since all groups of rats experienced a low mortality rate, indicating that the animals were in apparent good health during the study. In addition, a study by Hart (Toxicol Appl Pharmacol 82:281-291, 1985), in which rats were exposed to cadmium oxide at 1.6 mg/m^3, three hours per day, five days per week for six weeks, indicated that the effects mentioned by the commentor would resolve after a few weeks even while exposure continued. The exposure concentration used by Hart was 32 times higher than the highest concentration used by Takenaka, or 4 times greater if averaged over a 24-hour period. Thus, there is not sufficient evidence to suggest that lung defense mechanisms were overwhelmed during the Takenaka study.

Comment:

Ciba-Geigy stated that there are disproportionate changes in tumor incidence with successive dose halving in the Takenaka study. It appears likely that lower dosages caused less lung damage (considered a threshold event) and consequently fewer lung tumors. This would indicate that ambient airborne cadmium does not pose a carcinogenic risk to the general population and should not be classified as a toxic air contaminant.

Response:

As previously stated, the staff of DHS does not consider that there is sufficient evidence to link lung damage with the carcinogenicity of cadmium in rat lungs. Although there was an apparent dose-related increase in fibrosis in the lungs of treated animals (personal communication with Gunter Oberdorster), the severity of the lesions is unknown and a relationship, if any, between these lesions and lung cancer has not been determined. The staff of DHS does not consider a nonlinear dose-response curve in an animal study adequate evidence that a threshold process is responsible for carcinogenicity.

Comment:

Ciba-Geigy pointed out that cadmium compounds are not equivalent with respect to toxicity, absorption, distribution or excretion. Exposure to the two insoluble compounds, cadmium red and cadmium yellow, did not produce mortality and resulted in more rapid elimination, according to an unpublished study by Rusch. Other studies have also shown solubility and physical state of cadmium compounds to be important determinants of potency.

Response:

As stated in response to a similar comment by the Cadmium Council, Inc., the staff of DHS agrees that the toxic and possibly the carcinogenic potency of cadmium compounds could be related to their solubility. It

should be noted that cadmium carbonate and cadmium fume (oxide) were found by Rusch to be more toxic than the cadmium pigments. According to ARB, the carbonate and oxide forms of cadmium are more likely to be found in the ambient air.

Comment:

Ciba-Geigy stated that the doses in the Takenaka study imposed a lung burden on the rats that bears no relationship to effects expected from either larger amounts given for shorter periods or low-level ambient exposures of the general population.

Response:

The staff of DHS does not find the evidence cited by the commentor sufficient to indicate that the lung burden of cadmium imposed on the rats in the Takenaka study was unrepresentative of what might be expected from ambient exposure. Metallothionein levels probably do increase in response to cadmium exposure and it probably does act as a defense mechanism. Hart (1986) showed an increase in lung metallothionein over a six-week period during which the animals were receiving a daily dose four times the highest daily dose given to rats in the Takenaka study. During the six-week period initial lung lesions began to resolve, suggesting that metallothionein may decrease the toxicity of cadmium. There was no evidence that lung metallothionein synthesis was saturated during the Hart study. Thus, there is no reason to believe that rats in the Takenaka study were exposed to a cadmium concentration that would saturate this defense mechanism.

Department of Health Services

Responses to Public Comments on

Health Effects of Cadmium (Revised)

(June 1986 Draft)

Comment:

All 4 commentors (Ciba-Geigy, PG & E, Western Oil & Gas Association, and the California Council for Environmental and Economic Balance) raised the issue of thresholds in the cadmium risk assessment, and urged DHS to present a threshold model to provide a lower bound of risk. The EPA risk assessment of cadmium was cited for its presentation of both threshold and nonthreshold models.

Response:

The position of the Department of Health Services (DHS) with regard to the use of nonthreshold models is presented in the Guidelines for Chemical Carcinogen Risk Assessments and their Scientific Rationale (DHS, 1985):

> "...the DHS guidelines for risk assessment will not include the concept of 'thresholds' for carcinogenesis unless clear and convincing evidence is presented to demonstrate their existence for a specific carcinogen in specified circumstances"

The full discussion of thresholds from that document is attached and is incorporated by reference (Attachment A). The staff of DHS reiterates the arguments related to the mechanisms of cadmium-induced carcinogenicity in the responses to specific comments below:

Comment:

Ciba-Geigy contended that,

> "...the absence of a carcinogenic effect in the Thun study at the two lowest doses indicates that a threshold does exist even in the workplace and would exist for ambient air where exposure is a thousandfold less."

Response:

Lack of an elevated risk among workers in occupational cohorts exposed at low doses does not necessarily constitute evidence of a threshold, but rather evidence of the well-established "healthy worker effect". As explained in the document, these workers were estimated to have half the cancer risk of the U.S. population. Deaths from diseases of the circulatory system were also significantly lower than expected for the whole cohort (SMR=65), providing further evidence of a pronounced healthy worker effect in this cohort. In addition, the size of the study population was too small to detect the magnitude of risks expected at the low doses. Unless one compares the mortality to another worker population, the "expected" lung cancer deaths (obtained from the standard population, in this case 3.77) will be higher than what is predicted by the model at low doses (2.49 lung cancer deaths). This is because the number of expected cases is based on a population which differs from the study population on factors other than exposure to occupational carcinogens; correcting the "expected" for these differences yielded an adjusted value of 1.89 expected lung cancer deaths. Thus, taking into account the estimated healthy worker effect, this study had a power of less than 1% to reject a hypothesis of no-effect for the low dose group at the α=0.05 level, assuming the model predictions are correct. In other words, one would not have expected to detect an excess in lung cancer deaths in the low-dose group.

With regard to the EPA's risk assessment, neither of the models fitted by the EPA (the threshold or the nonthreshold model) fits the observed data as well as the model used by the DHS staff (Table C-1). The poorest fit was obtained by the threshold model for the low-dose group, where the model

fitted by the DHS staff was superior to both models presented by EPA. While all of these models were subject to the limitations of the data, the model that includes a parameter for the healthy worker effect is clearly a better specification of the quantitative dose-response relationship.

Comment:

In their comment on the threshold issue Ciba-Geigy stated:

> "It is of interest that your reviewers consider negative *in vivo* mutation studies as being insensitive tests as opposed to being indicative that the body can effectively handle small doses of cadmium; i.e., exhibit threshold characteristics, at concentrations that might be present in ambient air."

Response:

One interpretation of the results from these studies is that the body can effectively handle small doses of Cadmium. However, DHS staff members have concluded that in this case the interpretation is not valid because this type of assay is relatively insensitive; i.e., this assay is incapable of detecting other than large effects. The dominant lethal assay has a lower sensitivity than other genotoxicity assays because there is: (1) a relatively high rate of spontaneous lethal events that occur during development, and (2) the number of implants examined is extremely small compared to studies that examined individual cells for an effect. In addition, the DHS staff members agree with the International Agency for Research on Cancer (IARC, 1983) that it is difficult to rule out genotoxic effects based on short-term tests and there is insufficient evidence to justify creating a separate class of carcinogens (based on mechanism) for which different risk assessment methods would be used.

Comment:

Ciba-Geigy argued for the concept of a threshold for cadmium-induced carcinogenicity with the following:

> "First of all, excess cadmium can stimulate metallothionein synthesis which is known to detoxify cadmium following continuous low level exposure (Webb, M. (1979) in "Metallothionein", Kagi & Nordberg, editors, pp 313-20). Secondly, it is known that zinc and cadmium interact and compete for protein and enzyme binding sites."

Response:

As stated by the commentor, cadmium does induce metallothionein synthesis and this protein appears to have a protective role against cadmium toxicity. Hart (1986) showed that metallothionein increased during a six-week exposure period when rats were exposed to a cadmium oxide concentration of 1.6 mg Cd/m^3. Metallothionein, however, does not protect against acute cadmium toxicity (Webb 1979). Furthermore, Takenaka et al. (1983) showed that cadmium induced lung cancer at lower exposure levels than were used by Hart. Thus, metallothionein does not appear to prevent cadmium carcingenicity at exposure levels used in the Takenaka et al. study. Metallothionein may have a protective role, but it clearly cannot detoxify all cadmium that enters the body.

Zinc also appears to protect against cadmium toxicity. However, as with metallothionein, there is no evidence that zinc will protect an animal from the carcinogenic effects of cadmium below some specific exposure level. In addition, it is well established that a carcinogen's potency can be inhibited or enhanced by other compounds. Such effects do not indicate that a threshold therefore exists for carcinogenicity.

Comment:

The California Council for Environmental and Economic Balance (CCEEB) suggested that "the Air Resources Board needs to know the relative weight of the evidence regarding the plausibility of such thresholds."

Response:

In the case of cadmium, there is no compelling evidence that the carcinogenic effects are mediated by a threshold. This point is discussed at length in Part B Section VIII.

Comment:

PG & E contended that:

> "Although the DHS qualifies its estimate of 2-12 cases per million by stating that 'the actual risk may lie in or below that range', this is not sufficient since other experts have acknowledged that a zero risk estimate could be equally valid." (citing EPA, 1985)

Response:

The DHS staff believes that the presentation of the range of risk estimates as an upper bound is clear, and that the possibility of lower risk is sufficiently described in Part B, Section IX.

There is neither a theoretical basis nor empirical data sufficient to assign a probability to either the lower or upper bound region. Thus, it is not possible to give a relative weight to one or another portion within this range of risks. In the interest of protecting the public's health, and for reasons cited in Part B of the document and reiterated below, the DHS staff recommends that risk management decisions be based on the upper limit of this range: 30 excess lifetime cancer deaths per million persons from lifetime exposure to current average ambient levels of 2.5 ng/m^3 cadmium.

Comment:

CCEEB stated:

> "We can understand the basis for incorporation of the worst-case policy assumptions DHS uses to emphasize the maximum possible upper bound risk (although we believe that risk assessments should also present the 'most likely' risk estimate)."

Response:

As pointed out in Part B Section IX.2, this risk assessment does not present a worst-case scenario, but rather a plausible risk estimate, for the following reasons: (1) the estimate is based on the observed data and on realistic assumptions where data were lacking, both for exposure and for mortality in the study by Thun et al.; (2) the linear extrapolation model is, in the best scientific judgment of the DHS staff, a health-conservative method of extrapolation, while a worst-case would include a supralinear model; (3) the exposure estimate for California residents is based on mean levels obtained from monitoring throughout the urban areas of the state, not on the maxima; (4) as explained extensively in the document, the DHS staff recommends the human-based risk estimates, rather than the higher, animal-based estimates (Part B, Section IX.B.3). Thus, the estimated unit risk and its upper 0.95 confidence limit recommended by DHS provide a plausible range for the upper bound of risk, not a worst-case range.

Comment:

PG & E argued that the DHS risk assessment should recommend the "best" risk estimate rather than the "upper bound."

Response:

As discussed above, the DHS staff has presented a risk estimate based on plausible assumptions, not a worst-case scenario. The main source of

"health-conservatism" is in the use of a linear nonthreshold extrapolation model. The recommendation to use the upper bound on risk is based on two considerations: (1) as discussed in the document (Section VII.J.2), the risk estimate was based on lung cancer deaths only, whereas the epidemiologic evidence suggests urogenital cancer, as well. The data cannot be considered conclusive due to the small sizes of the study cohorts; nevertheless, the recommended risk estimate should provide an added margin of safety for possible increases in these cancers. (2) The application of a dose-response relationship observed in adult males to the general population assumes equal exposure and sensitivity across all ages and sexes. Since our risk assessment is based on average levels obtained at monitoring stations, this assumption could result in an underestimation of risk for several reasons:

The rapidly proliferating tissues of children may be more susceptible to carcinogenic agents than cells in adults. Second, where air concentrations of cadmium may be related to dust from contaminated soil, children are not only closer to the ground, but far more likely to play in dirt and thus to have substantially higher exposures than adults. Third, a recent paper by Phalen et al. (1985) showed that tracheobronchial particle deposition is generally more efficient in smaller (younger) individuals than in larger (older) people. For instance, the dose on a per kg basis for 5 μm diameter particles could be 6 times higher in a resting newborn than in a resting adult. This paper also showed that particle deposition varies with activity level. It appears, therefore, that at ages when individuals are potentially more susceptible to carcinogenic damage, they may be

consistently receiving higher exposures and distributing cadmium to the target site more efficiently.

For these reasons, the DHS staff does not concur with the conclusion of EPA (1985) that the upper bound risk estimate provides an "unnecessary added level of conservatism."

Comment:

Ciba-Geigy noted that the DHS staff did not take into account the potential effect of dose-rate on cadmium's carcinogenic activity, citing several studies.

Response:

The observations of Littlefield and Gaylor (1985), cited by the commentors, were based on the ED_{01} study of 2-acetylaminofluorene. Since the dose-rate characteristics of a compound's carcinogenicity may be dependent on the pathways for metabolic handling by the organism, this study does not necessarily apply to cadmium. The contrast between survival rates in the studies by Oldiges and Glaser (1986) and by Kaplan et al. (1977), also cited by the commentors, reflects a dose-rate effect of cadmium on noncarcinogenic toxicity, which may not generalize to carcinogenicity. Additionally, it is difficult to draw a conclusion based on a comparison of these two studies since they were done in different laboratories and with different strains of rats. DHS staff members, however, do recognize that dose-rate may influence the carcinogenic risks due to cadmium exposure. Because this effect has not been characterized quantitatively, the assumption was made that, in the absence of data, cumulative dose could define risk (Part B, Section IX.B.2). This is a health-protective assumption, since the environmental exposures involve much lower dose-rates,

as well as lower cumulative doses, than were used to estimate the carcinogenic potency of cadmium.

Comment:

Western Oil and Gas Association (WOGA) suggested that converting doses between species by direct air concentrations, i.e., not accounting for differences in metabolic rate, constituted manipulation of the data.

Response:

DHS staff conducted its animal-based risk assessment by converting rat to human doses on a surface-area basis. In the discussion comparing the animal- and human-based risk assessments, a risk estimate was derived in which direct air concentration in the animal experiment was taken to be equivalent to the human dose. As explained in Part B, Section IX.B.3, this calculation was presented for comparative purposes only, and does not, in the staff's opinion, constitute manipulation of the data.

Comment:

WOGA stated that the DHS staff's use of human data for the cadmium risk assessment is inconsistent with the previous use of animal data when human data were available for benzene.

Response:

The range of risk estimates (24×10^{-6} to 170×10^{-6}) recommended by DHS staff for the benzene risk assessment (DHS, 1984) was based on both the EPA estimate, which used data from three epidemiologic studies of leukemia deaths, and an estimate derived from a National Toxicology Program cancer bioassay in male mice. A comparison of the risk estimates and confidence intervals from the linear extrapolation using the best quality human data (Rinsky et al. 1981) and the multistage model using the most sensitive

animal data (preputial gland tumors in mice) shows both the point estimates and the upper 95% confidence limits (CL) to be very close:

RISK DUE TO 1 PPB AMBIENT EXPOSURE TO BENZENE

	Epidemiologic Data	Animal Data
Point Estimate	48×10^{-6}	78×10^{-6}
Upper 95% CL	120×10^{-6}	170×10^{-6}

Unlike benzene, for cadmium, the confidence intervals for the animal- and human-based risk estimates did not overlap. Therefore, the DHS staff felt that it was necessary to make a choice. For reasons stated at length in the document (Section IX.B.3), the choice to recommend risk estimates based on human data was dictated by both the quality of the epidemiologic data, (including the exposure information and the analysis of potential confounders) and our judgment that the assumptions were unlikely to result in an underestimate of the true risk. The approach taken by DHS staff for the cadmium risk analysis was therefore fully consistent with methods utilized in previous risk analyses.

Comment:

Ciba-Geigy stated that possible exposures to asbestos and to radon were not considered in the study by Thun et al. (1985) and that these could have been confounders. The commentor asserted that one of the lung cancer deaths was a worker who was also in another cohort where his death was attributed to asbestos.

Response:

It is possible that one of the workers in the study of Thun et al. may have left this plant and then worked elsewhere and received asbestos

exposure. Whether or not this is true, workers in the comparison population have similar opportunities to receive asbestos exposures. Since it is a relatively common exposure, asbestos-induced lung cancers contribute to the background rates throughout the U.S. Furthermore, if it is true that asbestos exposure contributed to the death of one of the cadmium-exposed workers, one cannot rule out an added contribution from cadmium, given the multifactorial nature of carcinogenesis. It is also unlikely that exclusion of this death would substantially alter the result of the risk assessment (e.g., compare the upper and lower portions of Table IX in Part B of the document). Dr. Thun, in a personal communication (9-9-86) indicated that in a further follow-up of the cohort to 1984, the lung cancer deaths continued to show a dose-response relationship to cadmium exposure.

The probability of significant radon exposures in the plant is low. The plant itself is above ground, so that if radon gas were emitted by soil, it would readily diffuse; containment such as occurs in mines or basements would not occur. If radon exposures were a problem in that region, one would expect a less pronounced effect when comparing to state rates as opposed to U.S. rates. The SMRs were higher, not lower, when the state rates were used as a comparison. Further, if radon daughters were being emitted from mill tailings in the walls, it would be highly coincidental if those portions of the plant where cadmium exposures were greater also had higher radon exposures.

While it is difficult to entirely rule out the potential for confounding from unmeasured sources such as radon and asbestos, the plausibility of these sources as explanations for the clear dose-response

between well-quantified cadmium exposures and excess mortality from lung cancer is low.

Comment:

Ciba-Geigy pointed out that the use of an occupational standard for cadmium to produce a safe ambient level yields a value which is three times as great as levels measured in "hot spots" in California, and fifty times as great as average ambient levels. The commentor cited Calabrese (1986) as saying that this method is "consistently more conservative or protective than that derived from actual data."

Response:

This method involves dividing the TLV (threshold limit value) by the ratio of hours in a workweek to total hours in a week, and then applying a safety factor of 100. The above quotation referred to 5 pollutants regulated by the U.S. federal government. In the same paper, Calabrese reported that this method applied to maximum acceptable occupational levels in the Soviet Union is more protective than the direct use of experimental data for 30 pollutants, and less protective for 13 others. Based on the figures provided by Ciba-Geigy for cadmium, this method is clearly less protective than the estimates EPA or DHS staff derived using the actual data. In the U.S., TLVs do not represent a uniform concept: they are principally based on considerations other than carcinogenicity, and may be based on practical considerations of what is attainable. In the case of cadmium, the ACGIH based its recommended TLV on kidney toxicity (ACGIH, 1982).

Comment:

Ciba-Geigy referred to evidence that cigarette smoking contributes to the body burden of cadmium, citing a study which showed that smokers' lungs contained a protein which binds cadmium.

Response:

DHS staff acknowledges that cigarette smoking can increase the cadmium body burden. It may contribute to the production of cadmium-binding proteins. However, this does not constitute evidence of the safety of ambient levels of cadmium. It is also possible that cadmium is one of the components of cigarette smoke which is responsible for its strongly carcinogenic effect.

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TABLE C-1

A COMPARISON OF THE OBSERVED DATA OF THUN ET AL.
AND THE PREDICTED RISKS FROM THREE MODELS

	Low	Middle	High	$\chi^2_{(df)}$*	p-value
OBSERVED:	2	7	7		
PREDICTED:					
EPA Nonthreshold Model	4.53	7.33	6.08	$1.6_{(2)}$	.45
EPA Threshold Model	3.77	4.61	7.00	$2.1_{(1)}$	.15
DHS Nonthreshold Model with Healthy Worker Effect	2.94	5.99	7.44	$0.5_{(1)}$	.48

* df=degrees of freedom

Issues in the Selection of Dose-Response Models

1. Thresholds

Traditional toxicology incorporates thresholds in the dose-response relationship. These are dose levels below which a toxicological response is not observed. This is not to imply that cellular or tissue damage does not occur below the "threshold" level, but rather that the organism either has the reserve capacity to withstand damage or is able to adapt to the toxicological stress. For toxicologic effects, a threshold is said to occur at dose levels that are insufficient to cause damage. For example, if a toxic substance killed nonreplicating optical neurons, sight would not suffer until a sufficiently large number (perhaps millions) of cells had died.

But the processes of carcinogenesis appear to be qualitatively different from those in classical toxicology. In contrast to the toxic effects described above which involve impairment of functions at the organ or organism level, the initial "target" for carcinogenic action is believed to be extremely small. As we develop a better understanding of the mechanisms of carcinogenesis and mutagenesis, it appears likely that many carcinogens interact with DNA or other target macromolecules. In addition, there is evidence that the occurrence of such events in a single cell can produce cancer.[28,29] The delivery of the critical molecules to critical cell at the critical time involves the interplay of a variety of protective defense systems within the body. However, there is some finite probability that a few molecules would evade these defenses and produce an event that triggers carcinogenesis. This scenario, so different from classic toxicologic processes, makes a threshold less likely for carcinogenesis.

Despite this, a pharmacokinetic argument has been made for the existence of practical operation thresholds. For example, the observation of a plateau of response at the high dose levels of the vinyl chloride dose-response curve is interpreted to mean that the enzyme system(s) that <u>activate</u> vinyl chloride to its carcinogenic species are overloaded or saturated. The argument is then made by analogy that protective enzymes systems that <u>deactivate</u> carcinogens and are reasonably effective at low doses may likewise be saturated and hence be less protective at the high doses encountered in animal bioassays.[30-34]

A model that produces a threshold in the dose-response curve has been developed. This model is based on the concept that high doses of carcinogens can overcome protective systems. However, this model produces a threshold by requiring that the carcinogen be instantaneously deactivated, which is unlikely. If detoxification reactions are not instantaneous, a small amount of the agent may escape detoxification by protective enzymes and interact with the DNA. In this instance, the protective effect of detoxifying enzymes would decrease the slope of the dose-response curve but would not produce a classical threshold.[35]

Even if thresholds could be determined for individuals, establishing a population threshold is more difficult because of the observed variability of the human population. This variation is a consequence of extreme genetic heterogeneity and differences in physiological state associated with age, sex, reproductive activities, nutrition, and exposure to environmental/ occupational stresses including other carcinogens. Even if it is assumed that each individual in the population has a threshold defined (at any one time) by his or her physiological state, the population is likely to be characterized by a very wide distribution of thresholds such that there may not be an absolute lower bound or population threshold.[6,36,37] Since the threshold dose for the human population should be the threshold dose for the most sensitive individual, this dose may be so low as to be effectively zero. By analogy, the threshold dose for an individual or organism is the threshold dose for the most sensitive cell, and this may also be extremely low.[38] Operationally, these variable threshold models are difficult to distinguish from nonthreshold models that are concave upward at low doses.

These models would produce absolute thresholds only under the assumptions of instantaneous deactivation and repair. Other models[39] predict nonlinearities in the dose-response curve that will lead to practical, but not absolute, thresholds. The presence, or absence, of an absolute threshold remains unconfirmable. The ED01 study indicated that the 2-AAF mouse exhibits an apparent threshold for bladder cancers at low doses. However, re-analysis of this low-dose data at greater resolution indicated that the threshold was more apparent than real: the incidence of bladder tumors increased with dose even at the low doses, and no threshold level could be determined.[9] Thus, scientists are now less concerned with the existence of thresholds than in the degree of nonlinearity of the dose-response curve in the low dose region.

Another factor against the existence of thresholds for carcinogens is the substantial "background" incidence of cancer in humans. Unless each carcinogenic substance operates by a unique mechanism, an additional small exposure to a substance may supplement an individual's exposure to other carcinogens operating by a similar mechanism. The high incidence of cancer of unexplained etiology demonstrates that human exposure is well in excess of any possible population threshold for at least some of these mechanisms. Viewed in this manner, since we cannot know which of the possible carcinogenic mechanisms are already operating and contributing to background incidence, we will assume that no additional exposure, however small, may be considered free of risk.

For these reasons, the DHS guidelines for risk assessment will not include the concept of "thresholds" for carcinogenesis unless clear and convincing evidence is presented to demonstrate their existence for a specific carcinogen in specified circumstances (NAS[6,7], OSHA[8], OTA[9], Food Safety Council[10,11]).

Memorandum

To : William Lockett, Chief
Office of External Affairs
Air Resources Board
1102 Q Street
Sacramento, CA 95812

Date : October 10, 1986

Subject: Response to Ciba-Geigy letter on Cadmium

From : Epidemiological Studies
and Surveillance Section
714 P Street
Sacramento, CA 95814

I have reviewed the comments and information contained in a letter addressed to Mr. Cliff Popejoy of the California Air Resources Board from Dr. Martin E. Bernstein of Ciba-Geigy Corporation dated June 18, 1986. I found the comments similar to those submitted earlier by Ciba-Geigy and the Cadmium Council. These comments point out that there is a difference in the toxic potency of various cadmium compounds probably due to the difference in solubility. In particular, cadmium sulfide is less toxic than cadmium oxide or cadmium chloride.

It is evident from the information submitted in this letter and in the earlier submissions that there is a difference in toxicity. In a previous set of responses (letter from Gary Murchison of ARB containing an addendum to the Draft Report on Cadmium, dated July 17, 1986), staff of the Department of Health Services indicated that such a difference does exist (pages 7 and 9).

I would like to point out that cadmium oxide, sulfate, and carbonate are considered the primary species of cadmium in ambient California air. Evidence indicates that these compounds act more like cadmium chloride, which was shown to be carcinogenic in an animal bioassay, than cadmium sulfide, which the commentor has indicated is less toxic than other cadmium compounds.

In the final paragraph of the letter, it was stated that no neoplastic lesions had been found in exposed animals that were part of the on going study cited in the letter. I believe it is premature to determine the adequacy of this study since the study is still in progress and the only pathology results appear to be for animals exposed for less than one year.

If you have any questions, please call me at 324-2829.

David M. Siegel, Ph.D.
Staff Toxicologist

cc: Michael Lipsett
Raymond Neutra

Oil, Chemical and Atomic Workers
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J. E. (JACK) FOLEY
DIRECTOR, DISTRICT NO. 1

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February 8, 1985

Mr. Peter D. Venturini, Chief
Stationary Source Division
AIR RESOURCES BOARD
1102 "Q" Street
Sacramento, California 95812

Dear Mr. Venturini:

In response to your communication regarding Cadmium that matter has been referred to our headquarters in Denver, Colorado Health & Safety Dept.

I would appreciate any request of this nature, in the future, be sent our Denver office, addressed as follows: Oil, Chemical and Atomic Workers International Union, Health & Safety Department, P.O. Box 2812, Denver, CO. 80201 to the attention of Director Dan Edwards with a copy to this office, as addressed on this letterhead.

Thank you for keeping us informed.

Very truly yours,

J.E. Foley
Director, District #1

JEF:rmm
cc: D. Edwards
File

emorandum

: Peter D. Venturini, Chief
tationary Source Division
r Resources Board
1102 Q Street
Sacramento, CA 95814

Date : February 13, 1985

Place : Sacramento

: **Department of Food and Agriculture**

ect: Request for Information Regarding Cadmium

Thank you for your letter regarding your information search on cadmium. Currently, only one pesticide containing cadmium is registered for agricultural use in California. Cleary's Granular Turf Fungicide which contains 0.75% cadmium (as cadmium chloride) is not widely used in California.

The Department has no additional health effects data on cadmium to contribute.

R. V. Peterson for

ori Johnston, Assistant Director
est Management, Environmental
Protection and Worker Safety
(916) 322-6315

cc Assemblywoman Sally Tanner
William V. Loscutoff, Chief, ARB
Alex Kelter, DHS

UNITED TECHNOLOGIES INMONT

Inmont Corporation

1255 Broad Street
P.O. Box 6001
Clifton, New Jersey 07015-6001
201/365-3400

February 13, 1985

Peter D. Venturini, Chief
Stationary Source Division
State of California
Air Resources Board
1102 Q Street
P.O. Box 2815
Sacramento, CA 95812

Dear Mr. Venturini:

Your request for information on cadmium was forwarded to me. I must report that we have no health effects information on cadmium. But, please add me to your mailing list to receive your information inquiries in the future.

Sincerely yours,

Eugene G. Wood

Eugene G. Wood
Manager,
Industrial Hygiene

EGW:mse

UNIVERSITY OF WASHINGTON
SEATTLE, WASHINGTON 98195

School of Public Health and Community Medicine
Department of Environmental Health, SC-34

February 12, 1985

William V. Loscutoff, Chief
Toxic Pollutants Branch
Re: Cadmium
California Air Resources Board
P.O. Box 2815
Sacramento, CA 95812

Dear Dr. Loscutoff:

Please find listed below several references on the developmental toxicity of Cadmium:

Barr, M: The teratogenicity of cadmium chloride in two stocks of Wistar rats. Teratology 7:237-242, 1973.

Chernoff, N.: Teratogenic effects of cadmium in rats. Teratology 8:29-32, 1973.

Cvetkova, R.P.: Materials on the study of the influence of cadmium compounds on the generative function. Gig. Tr. Prof. Zabol. 14:31, 1970.

Dencker, L.: Possible mechanisms of cadmium fetotoxicity in golden hamsters and mice: uptake by the embryo, placenta and ovary. J. Reprod. Fert. 44:461-471, 1975.

Levin, A.A. and Miller, R.K.: Fetal toxicity of cadmium in rat: Decreased utero-placental blood flow. Toxicol. Appl. Pharm. 58: 297-306, 1981.

Mulvihill, J.E.; Gamm, S.H. and Ferm, V.H.: Facial formation in normal and cadmium-treated golden hamsters. J. Embryol. Exp. Morphol. 24:393-403, 1970.

Thueraut, J.; Schaller, K.H.; Engelhardt, E. and Gossler K.: The cadmium content of the human placenta. Int. Arch. Occup. Environ. Health 36:19-27, 1975.

An excellent reference source for further information on the developmental toxicity of compounds is:

T.H. Shepard
Catalog of Teratogenic Agents
Johns Hopkins Press, Baltimore, 1984.

Several general references that you may want to include in your references are:

Hutton, M.: Sources of Cadmium in the Environment. Ecotoxic. and Environ. Safety. 7:9-24, 1983.

Itokawa, Y., Abe. T., Tabei, R., and Tanaka, S.: Renal and Skeletal Lesions in Experimental Cadmium Poisoning. Arch. Environ. Health. 28:149-154, 1974.

Korte, F. Ecotoxicology of Cadmium: General Overview. Ecotoxic. and Environ. Safety. 7:3-8, 1983.

Lauwerys, R.R., Buchet, J.P., Roels, H.A., Brouwers, J., and Stanescu, D.: Epidemiological Survey of Workers Exposed to Cadmium. Arch. Environ. Health. 28:145-?, 1974.

Lemen, R.A., Lee, J.S., Wagoner, J.K., and Blejer, H.: Cancer Mortality Among Cadmium Production Workers. Ann. N.Y. Acad. Sci. 271:273-?, 1976.

Rieth, F.H., Stocker, W.G., and Thiess, A.M.: Chromosome Investigations of Workers Exposed to Cadmium in the Manufacturing of Cadmium Stabilizers and Pigments. Ecotoxic. Environ. Safety. 7:106-?, 1983.

Quaife, C., Durnam, D., Mottet, N.K.: Cadmium hypersusceptability in C34 mouse liver: cell specificity and possible role of metallothionein. Tox. Applied Pharm. 76:9-17, 1984.

I hope this information is useful.

Sincerely,

Elaine Faustman-Watts

Elaine Faustman-Watts
Assistant Professor

EFW:jt

Ford Motor Company

The American Road
Dearborn, Michigan 48121

February 18, 1985

Mr. William V. Loscutoff, Chief
Toxic Pollutants Branch
Re: Cadmium and Asbestos
California Air Resources Board
P.O. Box 2815
Sacramento, CA 95812

Subject: Response to Mr. P. D. Venturini's Requests for Information Regarding Cadmium and Asbestos

Dear Mr. Loscutoff:

The Ford Motor Company has not undertaken independent scientific studies to evaluate the health effects relating to either cadmium or asbestos. Rather, the Company quantitatively measures the ambient concentrations within the plant environments of regulated and-suspected toxic air contaminants. These concentrations are evaluated with respect to the current Occupational Safety and Health Administration permissible exposure limits, National Institute of Occupational Safety and Health recommended standards, and American Conference of Governmental Industrial Hygienists Threshold Limit Values.

We regret that we are unable to submit information pursuant to your inquiries concerning health effects but we would like to continue to receive information on your progress in regulating toxic air contaminants.

Yours truly,

Frank P. Partee

F. P. Partee
Principal Staff Engineer
Air/Noise Compliance
Stationary Source Environmental
Control Office

10:DKJ7/L

UNIVERSITY OF CALIFORNIA, RIVERSIDE

BERKELEY • DAVIS • IRVINE • LOS ANGELES • RIVERSIDE • SAN DIEGO • SAN FRANCISCO SANTA BARBARA • SANTA CRUZ

COLLEGE OF NATURAL AND AGRICULTURAL SCIENCES
CITRUS RESEARCH CENTER AND
AGRICULTURAL EXPERIMENT STATION
DEPARTMENT OF SOIL AND ENVIRONMENTAL SCIENCES

RIVERSIDE, CALIFORNIA 92521

February 27, 1985

RECEIVED

MAR 4 1985

Stationary Source
Division
Air Resources Board

Mr. Peter D. Venturini, Chief
Stationary Source Division
Air Resources Board
1102 Q. Street
P.O. Box 2815
Sacramento, CA 95812

Dear Mr. Venturini:

This is a response to your request for information regarding cadmium. The following two articles published by the Department of Soil and Environmental Sciences, University of California, Riverside, CA, are submitted, herewith, for your consideration. Both papers dealt with environmental and biological transformations of cadmium:

1. Page, A. L. and A. C. Chang. 1979. Contamination of soil and vegetation by atmospheric deposition of trace metals. Phytopathology 69(9):1007-1011.

2. Page, A. L., M. M. El-Amamy and A. C. Chang. 1984. Cadmium in the environment and its entry into terrestrial food chain crops (to be published as Chap. 2 in a cadmium book; publisher Springer-Verlag, New York, N.Y.).

Sincerely,

A. C. Chang

ACC:jt
Enclosures

cc: M. M. El-Amamy
A. L. Page

Cadmium Council, Inc.
292 Madison Avenue
New York, N.Y. 10017

212 578-4750

February 28, 1985

Lynn Terry
Stationary Sources Division
Air Resources Board
1102 Q Street
P.O. Box 2815
Sacramento, CA 95812

Dear Ms. Terry,

I am sorry for the delay in responding to your request but the Yost and Greenkorn study was being printed. I have also included the proceedings from the Second, Third, and Fourth International Cadmium Conferences, a book entitled Cadmium Chemicals, and an article, "The Effect of Cadmium on the Environment" by J. F. Cole and R. A. Volpe.

I will gladly carry out a data search for you if you need further information. I will be calling you shortly to see ~~if~~ I may be of further assistance.

Sincerely,

Giovina L. Leone
Assistant Director
Environmental Regulations

mfcl

enclosures

DEPARTMENT OF THE ARMY
U. S. ARMY ENVIRONMENTAL HYGIENE AGENCY
ABERDEEN PROVING GROUND, MARYLAND 21010-5422

REPLY TO ATTENTION OF
Occupational and Environmental
Medicine Division

MAR 12 1985

William V. Loscutoff
Chief, Toxic Pollutants Branch
California Air Resources Branch
P.O. Box 2815
Sacramento, California 95812

Dear Mr. Loscutoff:

While the US Army Environmental Hygiene Agency does not conduct research into the toxicology of cadmium, we are aware of an EPA draft document, not included in your bibliography, which you may wish to review. The title is: Updated Mutagenicity and Carcinogenicity Assessment of Cadmium, Addendum to the Health Assessment Document for Cadmium (May 1981, EPA-600/8-81-023), EPA-600/8-83-025B, April 1984, External Review Draft. This document is available from the National Technical Information Service.

Any comments should be directed to Major Robert W. Petzold, M.D. at this Agency.

Sincerely,

Joel C. Gaydos

Joel C. Gaydos
Colonel, Medical Corps
Director, Occupational and
Environmental Health

DCMA
DRY COLOR MANUFACTURERS' ASSOCIATION

Representing the Color Pigments Industry

SUITE 202, 206 NORTH WASHINGTON STREET
ALEXANDRIA, VA 22314 (703) 684-4044
Mailing Address:
P.O. BOX 931, ALEXANDRIA, VA 22313

March 29, 1985

William V. Loscutoff, Chief
Toxic Pollutants Branch
Re: Cadmium
California Air Resources Board
P.O. Box 2815
Sacramento, CA 95812

Dear Sir:

Subject: Request for Information Regarding Cadmium

The Dry Color Manufacturers' Association (DCMA) appreciates receiving from the California Air Resources Board their request to furnish information on the health effects of cadmium.

The DCMA is an industry trade association representing small, medium and large pigment color manufacturers throughout the United States and Canada, accounting for approximately 95% of the production of color pigments in these countries. Included within the DCMA structure is the Cadmium Pigments Committee (the "Committee") which is composed of major manufacturers of cadmium pigments.

The Committee has been active for many years in addressing safety and health concerns with respect to cadmium pigments. It has provided information to interested government agencies and to the public with respect to these concerns. In addition, the Committee has sponsored various testing activities and studies conducted by consulting professors, laboratories and institutions. Consequently, the Committee is generally recognized as the primary source of expert industry information on cadmium pigments, including safety and health concerns. The Committee is vitally interested in any development that might affect the use of these important color pigments.

While the Committee has undertaken animal studies to demonstrate that cadmium pigments, owing to their insolubility, are less bio-available than more soluble cadmium compounds both by ingestion and inhalation, no studies have been undertaken by the Committee that relate to levels of cadmium in the atmosphere over urban and rural areas.

It is noted that the list of references on cadmium enclosed with your letter of February 4, 1985 does not include a comprehensive review of environmental levels of cadmium prepared by Dr. Kenneth J. Yost of Purdue University, West Lafayette, Indiana entitled "Cadmium, the Environment and Human Health: An Overview" (Experientia 40 (1984) Birkhauser Verlag CH-4010 Basel/Switzerland). A copy is enclosed. Taking into account the production of cadmium, its major uses and disposal into the environment, this report concludes that "respiratory (inhalation) intake of cadmium by urban populations is negligible".

You are no doubt aware of the data available on ambient air levels of cadmium in Section 4.2.1 of the U.S. Environmental Protection Agency "Health Assessment Document for Cadmium" prepared by L.D. Grant, et al. and dated October 1981 (EPA 600/8-81-023). With few exceptions the average annual cadmium levels for U.S. cities studied fall within a range of 1 to 20 nanograms/cubic meter of air. From these values it has been estimated that cadmium in the ambient air contributes less than 2 micrograms per day of an adult's uptake of cadmium as compared to from 20 to 50 micrograms per day by way of the diet.

You may find of interest the enclosed booklet published by the Committee several years ago entitled, "Cadmium Pigments - An Encouraging Outlook".

It is understood that the health evaluation report to be prepared by the ARB staff for submission to a Scientific Review Panel will be made available to the public. Your sending us a copy of this report when available or advising us how to obtain a copy will be very much appreciated.

Sincerely,

J. Lawrence Robinson
Executive Vice President

Enclosures (Yost Paper and "Cadmium Pigments - An Encouraging Outlook")

cc: Peter D. Venturini, Chief
Stationary Source Division
State of California
Air Resources Board
P.O. Box 2815
Sacramento, CA 95812

PACIFIC GAS AND ELECTRIC COMPANY

PG&E — 77 BEALE STREET • SAN FRANCISCO, CALIFORNIA 94106 • (415) 781-4211 • TWX 910-372-6587

April 16, 1985

Mr. William V. Loscutoff, Chief
Toxic Pollutants Branch
RE: Cadmium
California Air Resources Board
P.O. Box 2815
Sacramento, CA 95812

Dear Mr. Loscutoff:

Request for Public Health
Information Regarding Cadmium

Pacific Gas and Electric Company received your February 4, 1985 request for additional public health information regarding Cadmium. We reviewed the bibliography and concluded that we are unaware of any additional information which would be of use to you.

PGandE would like to remain on the Cadmium mailing list, and would appreciate receiving copies of future announcements on reports. Please send future communications to me at:

Pacific Gas and Electric Company
77 Beale Street - Room 1357
P.O. Box 7640
San Francisco, CA 94124

Thank you.

Sincerely,

J. F. McKENZIE

STATE OF CALIFORNIA — GEORGE DEUKMEJIAN, *Governor*

DEPARTMENT OF FOOD AND AGRICULTURE

1220 N Street
Sacramento
95814

April 22, 1985

William V. Loscutoff, Chief
Toxic Pollutants Branch
California Air Resources Board
P.O. Box 2815
Sacramento, CA 95812

Dear Mr. Loscutoff

Subject: Public Records Request
Our File PR-85-05

Enclosed please find the data on cadmium requested in your letter of February 4. Mr. Bill Erdman of Mallinckrodt Inc. has indicated his company will not respond to our letter of February 27. Accordingly, the two studies are being released.

Sincerely

Lisa Brown, Staff Counsel
Pesticide Enforcement Unit
(916) 445-5895

cc Bill Erdman
Alex Kelter, DHS
Lori Johnston, CDFA
Wayne Morgan, President CAPCOA
Jan Bush, Executive Secretary, CAPCOA
David Howekamp, EPA Region IX
Assemblywoman Salley Tanner
Senator Ralph Dills
Senator Art Torres
Emil Mrak, Chair, SAP

APPENDIX B

HEALTH EFFECTS REQUEST TO DHS AND LETTER OF RESPONSE

Memorandum

To : Kenneth Kizer, M.D., Director
Department of Health Services
714 P Street
Sacramento, CA 95814

Date : April 12, 1985

Subject: Evaluation of Cadmium

From : James D. Boyd
Executive Officer
Air Resources Board

I am writing to formally request that the Department evaluate the health effects of cadmium as a candidate toxic air contaminant in accordance with Assembly Bill 1807 (Tanner). According to Health and Safety Code Sections 39660-62, your Department has ninety days to submit a written evaluation and recommendations on the health effects of cadmium to the Air Resources Board and may request a thirty day extension.

Attached for your staff's consideration in evaluating cadmium are: Attachment I - a suggested list of topics that we believe should be included in your cadmium evaluation and recommendations; Attachment II - a list of references on cadmium health effects which were identified in an ARB letter of public inquiry or received in response to the inquiry letter; and Attachment III - ambient cadmium concentration data which should be used to estimate the range of risk to California residents as required in Health and Safety Code Section 39660(c).

My staff is available for consultation in conducting this health effects evaluation. We look forward to continuing to work closely with you and your staff in carrying out this legislative mandate. If you have any further questions regarding this matter, please contact me at 445-4383 or have your staff contact Peter D. Venturini, Chief of the Stationary Source Division, at 445-0650.

Attachments

cc: Gordon Duffy
Alex Kelter, DHS, w/attachments
Raymond Neutra, DHS, w/attachments
Peter D. Venturini, ARB
Assemblywoman Sally Tanner
Claire Berryhill, DFA
Emil Mrak, Chairman and Members
of the Scientific Review Panel
Senator Ralph Dills
Senator Art Torres
John Holmes, ARB

ATTACHMENT I
Suggested List of Topics

CADMIUM

I. Chemical and Physical Properties
   A. Cadmium compounds
   B. Production and use
   C. Occurrence
      1. Natural
      2. Airborne, water, soil
      3. Cigarette Smoke
      4. Occupational
      5. Plant Uptake
      6. Food

II. Acute Health Effects
   A. Acute pulmonary toxicity
   B. Chronic renal damage (see Section V)

III. Carcinogenicity
   A. Epidemiologic evidence
      1. Lemen study (1976). Cohort of 292 workers in cadmium production facility. An excess of malignant respiratory disease found as was an excess of cancer of the prostate.

      2. Varner study (1983). An enlarged version of the Lemen study that demonstrated dose-response relationships for both lung cancer and total neoplasms.

      3. Thun study (1984). Cohort of Lemen expanded to 602 white males with at least 6 months work in cadmium production between 1940 - 1969. This cohort was followed through 1978. Mortality from cancer of the respiratory tract (but not the prostate) was significantly greater in the cohort than the general population (2:1). Cancer mortality increased with an increase in exposure. Thun considered both possible confounders of arsenic and smoking and dismissed both.

4. Other epidemiologic studies: Sorahan et al., 1983; Armstrong et al., 1983, 1982; Holden H., 1980; providing limited additional epidemiologic evidence for excess lung cancer mortality.

5. C. A. G.: Further evidence provided by CAG under the assumption that arsenic is additive to the risk of lung cancer from cadmium while smoking is multiplicative indicates that the upper bound for the expected number of lung cancer cases is still significantly below that of the observed number of cases at the $P < 0.05$ level in the Thun study.

6. NIOSH: Cadmium is a potential occupational carcinogen.

7. IARC: The human epidemiologic evidence appears to provide limited evidence of lung cancer risk from exposure to cadmium. (conclusion prior to Thun study).

B. Animal evidence

1. Takenaka et al. study, 1983. Exposure of rats to cadmium chloride aerosol by inhalation was done over the lifetime of the animals. A positive dose-response relationship for the development of primary lung carcinoma was shown. 25 out of 35 rats (71.4%) exposed to 50 ug/m^3 cadmium chloride aerosol developed lung cancer compared to 0 out of 38 unexposed controls. 20 out of 38 (52.6%) exposed to 25 ug/m^3 and 6 out of 39 (15.4%) exposed to 12.5 ug/m^3 developed lung cancer.
2. Additional animal studies contributing information to the carcinogenic potential of cadmium.

   a. Lung cancer in rats by single inhalation exposure (Hadley et al., 1979).

b. Mammary tumors in males by multiple tracheal instillation (Sanders et al., 1984).

c. Pancreatic Islet cell tumors following parenteral administration of cadmium chloride (Poirier et al., 1983).

d. Prostate tumors by injections of cadmium chloride into prostate (Scott and Aughey 1979)

e. Interstitial-cell tumors of the testis observed following testicular atrophy in rats and mice given s.c. injections of soluble cadmium salts, cadmium sulphate and cadmium chloride (Gunn 1964 and 1963).

f. Local spindle-cell sarcomas in Wistar rats by single s.c. injections of cadmium chloride, sulphate, sulfide, and oxide (Knorre, 1970).

C. Short-term tests for genotoxicity

1. Gene mutation on DNA damage in bacteria or fungi

a. Data is conflicting. Negative results reported by Heddle and Bruce 1977, Milvy and Kay 1978, Polukhina et al. 1977, Putrament et al. 1977.

b. Positive results reported by Hedenstedt et al. 1979, Nishioka 1975, and Kanematsu 1980, Takahashi 1972.

2. Gene mutations in mammalian cell cultures

a. Mouse lymphoma assay - mutagenic by Amacher and Paillet, 1980. Also positive results by Oberly et al. 1982.

b. Chinese hamster cell assay

Mutagenic results reported by Casto (1976). Ochi and Ohsawa (1983) demonstrated single strand DNA scission by cadmium indicating formation of DNA-protein cross-linking by cadmium.

3. Studies of cadmium mutagenesis via sex-linked recessive lethal test in Drosophila Melanogester

   a. Majority of studies show no mutagenic response.
   b. Dominant lethal test in Drosophila resulted in a positive response with a dose-response relationship.

4. Chromosomal aberrations

   a. In human lymphocytes and human cell lines results have been conflicting and contradictory.

   b. Chinese hamster cells - Chromosomal aberrations followed treatment with cadmium.

   c. Mouse carcinoma cells - no aberrations noted following cadmium treatment.

   d. No observed chromosomal aberrations in bone marrow cells of rodents treated with cadmium.

   e. Plants exposed to cadmium demonstrated chromosomal aberrations and gene mutations.

   f. Cadmium is a mutagen that interfers with spindle formation in vitro and in vivo studies in mammals.

   g. Cadmium induces aneuploidy in CHO cells and in whole mammals and germ cells of female mice and Syrian hamsters.

h. Numerical aberrations induced by cadmium chloride in female germ cells of mice are inherited in embryos.

IV. Reproductive Effects

A. Animal studies

1. Testicular damage by cadmium in mice (Gunn et al. 1965, Parizek 1960)

a. Pretreatment of mice with zinc reduces incorporation of cadmium into spermatids.

b. Cadmium inhibits incorporation of Thymidine into spermatogonia-(significant reduction of litter size by injection of 1 mg/kg b.w. cadmium chloride into male mice 15 to 48 days before mating with untreated female mice)

c. Destruction of testicular cells (spermatogenic and interstitial) of rabbits given 1 to 8 s.c. injections of 9-18 mg/kg b.w. cadmium chloride.

d. One s.c. injection of 0.05 mmol/kg b.w. (9.2 mg/kg b.w.) cadmium chloride into rabbits produced aspermia within 4 weeks with no recovery. (Paufler and Foote, 1969).

e. Schroeder and Mitchner (1971) exposed mice for 3 generations to cadmium in drinking-water (10 ug/ml) which produced a reduction in litter size in breeding mice with loss of strain characteristics after two generations and congenital anomalies.

f. Teratogenesis in rats by daily oral administration of 20-80 mg/kg b.w. cadmium chloride days 6 to 19 gestation. (Scharf et al 1972).

g. Teratogenesis in golden hamsters by i.v. injection of 2-4 mg/kg b.w. cadmium sulphate on day 8 of gestation produced cleft lips and palates and other facial defects (Ferm and Carpenter 1968). Also in rat by Barr, 1973; Chernoff, 1973 and Ishizu et al, 1973.

h. Necrosis and blood clot formation of placenta with fetal death 24 hours after s.c. injection of cadmium salt into rats on one of days 17-21 of pregnancy (Parizek, 1964).

i. Exposure to very low doses of Cd by inhalation did not demonstrate teratogenesis.

B. Human Studies

a. Sex differences: multiparous post-menopausal women in Fuchu, Japan develop itai - itai disease (Tsuchiya, 1969) characterized by elevated cadmium blood levels and osteomalacia (proximity to cadmium mine).

b. Placental transfer: Lauwerys, Bachet, Rolls and Hubermont-a series of papers on cadmium levels in Belgim women in placenta, maternal and cord blood between 1975 - 1976. Results suggest a partial placental barrier to cadmium transfer. Cadmium crosses the placenta and levels in the fetus are generally slightly less than in maternal blood. Results in smokers suggest cadmium from smoking may induce metallothionein synthesis in the placenta which can bind cadmium and protect the fetus.

c. Study of Tsvetkova, 1970, showing no effect on the menstrual cycle in 106 women working with cadmium.

d. There is limited evidence that reported exposure to very high levels of cadmium may induce testicular damage in men. (Smith et al, 1960 and Favino et al, 1968).

V. Pharmacokinetics and Toxicity

A. Animal studies - toxicity

1. LC_{50} in dogs of cadmium chloride mist: 0.32 mg/cadmium/l of air for 30 minute exposure. (Harrison et al., 1947)

2. LD_{50} in mice, rats, guinea pigs, rabbits, dogs and monkeys of cadmium oxide fumes for 10-30 minutes were < 700, 500, about 3500, about 2500, 4000 and 15,000 min-mg/m^3, respectively (Barrett et al., 1947). 11% retention of cadmium oxide by the lungs of these animals.

3. Snider et al. (1973) produced emphysema experimentally in male rats exposed to cadmium chloride aerosols (0.1% solution) for 1 hour per day for 5-15 days.

4. Cadmium damages testes of experimental animals (see section IV).

5. Several experiments in rats (Friberg et al., 1974, 1975) show kidney tubular damage when the concentration in the kidney cortex is about 200 ug/g wet weight.

6. Hypertension has been produced in rats given cadmium in drinking water (5 ug/ml Cd) for long periods of time (Kanisawa & Schroeder, 1969; Perry and Erlanger, 1974).

7. Cadmium may produce zinc deficiency (Petering et al., 1971)

8. Large doses of zinc prevent toxic action of cadmium on testes (Friberg et al., 1974)

B. Animal studies -pharmacokinetics

1. Biological half-life of a single oral dose of cadmium in female mice was estimated to be 200 days (Richmond et al., 1966).

2. Following inhalation 10 to 40% of Cadmium is absorbed, primarily in the lung and additionally by the gastrointestinal tract after mucocilliary clearance.

3. Absorbed cadmium in rats is first transported to the liver and slowly transferred to the kidney. Only 1 to 2% of absorbed cadmium is excreted via the urine or feces. Metallothionein (a low mol. wt. protein) found in the liver, red cells, plasma and duodenal mucosa of several species is thought to play an important role in transport of cadmium in the body. (Norberg, 1971; Friberg et al., 1974). Calcium and iron deficiencies enhance the absorption and tissue retention of cadmium.

C. Man: toxicity and pharmacokinetics

1. Long term exposure of man to large amounts of cadmium by inhalation or ingestion eventually causes renal tubular dysfunction (Holden, 1969; Piscator, 1962; Potts, 1965). Osteomalacia may result from disturbances in mineral metabolism (Adams et al, 1969; Friberg, 1974).

2. Cadmium's role in human hypertension causation is uncertain (Friberg et al., 1974)

3. About 5% of ingested cadmium is absorbed (Rahola et al., 1972; Yamagata et al., 1974) and remainder is excreted in feces. Non-exposed subjects excrete 10-60 ug daily in feces (Wester, 1974).

4. Cadmium is stored with metallothionein in the liver and kidneys. One-third of body burden occurs in the kidneys (Friberg et al., 1974).

5. Newborn is practically free from cadmium (Schroeder et al.; 1961).

6. Normal levels in kidney cortex at age 50 ranges from 15-30 ug/g. (Friberg et al.; 1974)

7. Smokers have higher (5-100%) renal concentrations of cadmium than do non-smokers (Lewis et al., 1972)

8. Urinary excretion of cadmium is 1-3 ug/day in adults. Smokers excrete more (Piscator, 1976).

9. Biological half-life of cadmium in man is 10-30 years (Elinder, et al., 1976).

VI. Risk Assessment: (Review Articles: U.S. EPA Draft-[April, 1984] Updated Mutagenicity Assessment of Cadmium)

A. Quantitative estimation of risk

1. Unit risk for cadmium in air (lifetime-cancer risk occurring in a hypothetical population in which all individuals are exposed continuously from birth throughout their lifetimes to a concentration of 1 ug/m^3 of the agent in the air they breathe)

2. Potency of cadmium relative to other carcinogens that CAG has evaluated.

3. Data for quantitative estimation of risk taken from:

   a. Lifetime animal studies or

   b. Human studies where excess cancer risk has been associated with exposure to the agent.

   c. Mutagenicity studies of irreversible damage to DNA. (Quantal type of biologic response characteristic of

mutagenesis is associated with a linear non-threshold dose-response relationship).

B. Dose-response assessment based on:

1. Available animal data
2. Human epidemiology and monitoring
3. Workplace evidence

C. Range of potential risks

1. Unit risk estimate based on animal study of Takenaka et al. (1983) using male Wistar rats and cadmium chloride inhalation exposure over lifetime of rat with dose-response relationship shown.

2. Unit risk estimate based on a human study.

   Study of Thun et al. (1984). Cohort of cadmium smelter workers hired on or after January 1, 1926, and employed for at least 2 years in a production capacity in the same plant from January 1, 1940 to December 31, 1969 developed 16 cases of respiratory cancer deaths through December 31, 1978. (Only 6.99 would be expected).

ATTACHMENT II

Cadmium References (1/24/85)

1. Amacher, D. E and Paillet, S. C. (1980) Induction of trifluorothymidine-resistant mutants by metal ions in L5178Y/TK+/- cells. Mutat Res . 78 (3):p279-88

2. Anderson, L. D et al (1983) Updated mutagenicity and carcinogenicity assessment of cadmium: addendum to the health assessment document for cadmium (May 1981) EPA Report. EPA-600/8-83-025A:151pp.

3. Anonymous (1981) Role of metals in carcinogenesis. Problems of epidemiological evidence. Environ Health Perspect. 40:11-20.

4. Baranski, B., Opacka, J., Wroinska-Nofer, T., Trzcinka-Ochocka, M., Sitarek, K. and Matczak, W. (1983) Effect of inhalation exposure to cadmium oxide on arterial blood pressure, lipid metabolism and tissue cadmium concentration in rats.. Med Pr 34(1):11-9.

5. Baranski, B., Stetkiewicz, I., Trzcinka-Ochocka, M., Sitarek, K. and Szymczak, W. (1982) Teratogenicity,fetal toxicity and tissue concentration of cadmium administered to female rats during organogenesis.. J Appl Toxicol (UNITED STATES) . 2 (5) :p255-9.

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4. Submitted by Joel C. Gaylos. U.S. Army Environmental Hygiene Agency, Aberdeen Proving Ground, Maryland.

Updated Mutagenicity and Carcinogenicity Assessment of Cadmium, Addendum to the Health Assessment Document for Cadmium (May 1981, EPA-600/8-81-023), EPA-600/8-83-025B, April 1984.

5. Submitted by Larry Sweetser, Sanitary Fill Company, San Francisco:

Friberg, Lars, 1979. Handbook of Toxicology of Metals, North Holland Biomedical Press.

ATTACHMENT III

Ambient Cadmium Concentrations and Emission Trends

Data from the U.S. Environmental Protection Agency's National Aerometric Data Bank for the 1964 to 1985 period show mean cadmium concentrations between 0 (below detectable limit) and 125 ng/m^3. At stations where more than 50 percent of the samples were above the detection limit for sampling periods between 1976 and 1984, mean cadmium concentrations ranged from 0.4 to 3.0 ng/m^3. These data represent total particulate cadmium 50 um and smaller collected from ambient air at sites throughout California.

Cadmium or its compounds are used in the production of pigments, alloys, and nickel-cadmium batteries, as stabilizers for plastics, and in cadmium plating. Potential sources of cadmium in air are emissions from secondary non-ferrous smelting, secondary steel production, fossil fuel combustion, refuse and sewage sludge incineration, cadmium electroplating, and manufacturing of cadmium-containing products. Investigations are under way to determine the magnitude of emissions in California from these and other types of sources.

United States demand for cadmium is expected to increase at an average annual rate of 1.8 percent through 1990.

tate of California — Department of Health Services

Memorandum

To : James Boyd
Executive Officer
Air Resources Board
1102 Q Street
Sacramento, CA 95814
B-4

Date : July 17, 1985

Subject: Request for Extension of Cadmium Health Evaluation

RECEIVED
JUL 24 1985

From : Office of the Director
8/1253 5-1248

Due to the expected arrival of recently updated information on cadmium from the U.S. Environmental Protection Agency, we are requesting a 30-day extension to August 9, 1985 for submission of the cadmium document.

Kenneth W. Kizer, M.D., M.P.H.
Director

RECEIVED
JUL 24 1985
Stationary Source
Division
Air Resources Board

Received 7 24 85

State of California

xc: RV

Department of Health Services

Memorandum

James Boyd, Executive Officer
Air Resources Board
1102 Q Street
Sacramento, CA

Date : August 14, 1985

Subject: Cadmium Document

RECEIVED

AUG 1 [illegible]

Stationary Source Division
Air Resources Board

From : Office of the Director
714 P Street, Room 1253
Sacramento, CA

I have been informed the Department of Health Services will be unable to meet the August 9, 1985 due date for submission of the cadmium document because it has taken longer than anticipated to complete the document. It is expected to be completed by August 23, 1985. We are requesting an extension until August 26, 1985. Thank you for your patience.

Maridee Gregory M.D.

Maridee Gregory, M.D.
Acting Deputy Director
Public Health

cc: Kenneth W. Kizer, M.D., M.P.H.
Alex Kelter, M.D.
Donald Lyman, M.D.

RECEIVED

AUG 16 1985

Stationary Source Division
Air Resources Board

State of California — Department of Health Services

Memorandum

To : James D. Boyd
Executive Officer
Air Resources Board
1102 Q Street
Sacramento
B-4

Date : October 10, 1985

Subject: Health Effects of Cadmium

From : Office of the Director
8/1253 5-1248

Attached is the document prepared in response to your memo requesting the assistance of the Department of Health Services in evaluating the health effects of cadmium.

Kenneth W. Kizer, M.D., M.P.H.
Director

Attachment

cc: C. Berryhill - w/o attachment
J. Sharpless - w/o attachment
Assemblymember Tanner - w/o attachment
P. Venturini - w/o attachment

10/10/85

APPENDIX C

DISCUSSION OF EMISSION ESTIMATES

APPENDIX C

I. STATIONARY SOURCES

1. Cadmium Plating:

There are 31 cadmium platers in the South Coast Air Basin which emitted 0.22 ton of cadmium in 1982. The ratio of cadmium platers to chrome platers in the South Coast Air Basin is approximately 0.20 to 1.0 (Zwiacher et al., 1983, pp. 207-214). It is estimated that there are 400 chrome platers in California (CARB, 1985). Assuming the ratio of cadmium to chrome platers in the state is the same as in the South Coast, approximately 80 cadmium platers are operating in California. Cadmium emissions from this source are estimated as follows:

EMS = (80 platers/31 platers) (0.22 ton/year) = 0.57 ton/year

2. Coal Combustion: (Sierra Energy & Risk Assessment, Inc., 1982).

a. Cement Manufacturing:

* Consumption in 1984 = 1,600,000 tons
* Emission factor = 2.03×10^{-4} lb. Cd/ton (Krishnan, et al., 1982)
* Ems = (1,600,000 tons/yr) (2.03×10^{-4} lb Cd/ton) (ton/2,000 lbs) = 0.16 ton/yr

b. Cogeneration:

* Consumption in 1981 = 240,000 tons
* Emission factor = 1.3×10^{-4} lb. Cd/ton (Krishnan, et al., 1982)
* Ems = (240,000 tons/yr) (1.3×10^{-4} lb Cd/ton) (ton/2,000 lbs) = 0.02 ton/yr

b. Sugar Beet Processing:

* Consumption in 1981 = 25,000 tons
* Emission factor = 9.1×10^{-4} lb. Cd/ton (Krishnan et al., 1982)
* Ems = (25,000 tons/yr.) (9.1×10^{-4} lb Cd/ton) (ton/2,000 lbs.) = 0.01 ton/yr.

Together, cadmium emissions from coal combustion amounted to 0.19 ton in 1981.

3. Residual Oil:

California burned approximately 1.44 billion gallons of residual oil in 1984 (CARB, 1986a; CARB, 1986b). Of this, utilities burned approximately 16 percent at their power plants. One utility, Southern California Edison (SCE) used only 2.2% of the residual oil burned (CARB, 1986a; CARB 1986b; CARB 1986c). Emissions for residual oil combustion were estimated using cadmium concentrations of fuel oil reported by SCE and Pacific Gas and Electric Company (PG&E) (SCE, 1986; PG&E, 1986), and the amount of residual oil burned in California (CARB, 1986a).

	SCE	PG&E
Cadmium concentration (ppm)	0.01	0.31-0.52

Assuming all cadmium in the residual oil is emitted into the atmosphere upon combustion, cadmium emissions were estimated as follows:

a. Utility Boilers:

California utilities used approximately 232.3 million gallons of residual oil in 1984 (CARB, 1986a). Cadmium emissions from residual oil burned at utilities are estimated using equation I.

$$EMS = PR * D * C_c * U_f^{-1} \qquad (1)$$

Where:

Ems = cadmium emissions, tons per year

PR = Process Rate, millions of gallons/year

D = Density of residual oil (8.2 lb./gal.), lb./gal.

C_c = Cadmium concentration of residual oil, ppm

U_f = Unit conversion factor (2000), lb./ton

	Lower (tpy)	Upper (tpy)
Ems	0.01	0.50

Note: Data on cadmium concentration from SCE were used to estimate the lower number while the highest cadmium concentration in fuel oil as reported by PG&E was used to estimate the upper number.

b. Other Sources:

Besides being used at utilities, residual oil is used in chemical manufacturing and oil and gas extraction activities and in ships. In 1984, approximately 1.21 billion gallons of residual and/or crude oil were used by such sources (CARB, 1986a; CARB,

1986b). Because the SCE fuel cadmium content data are only applicable to the South Coast utilities and refineries (probably only SCE, because SCE used foreign oils with very low sulfur content, 0.17% to 0.18% (Stepman, 1986), and because the South Coast industries only used approximately 0.6 percent (CARB, 1986a; CARB, 1986b; CARB, 1986d; CARB, 1986e) of total residual oil burned by sources in this category, only data from PG&E are used to estimate cadmium emissions. Equation I is also applicable for this category. Estimated cadmium emissions are as follows:

	Lower (tpy)	Upper (tpy)
Ems	1.5	2.6

Adding emissions for utility boilers to that for other sources, the statewide cadmium emissions from residual oil combustion are estimated to range from 1.5 to 3.1 tons in 1984.

4. Secondary Smelters:

   a. Copper:

      The California Emission Data System identifies 71 copper smelters in California. Together, these facilities consumed 54,100 tons of copper scrap in 1981 (CARB, 1985c). An uncontrolled emission factor of 3 lbs. Cd/ton of copper scrap was reported (Coleman, R., 1979). Assuming 90 percent control, cadmium emissions from these copper smelters are:

      Ems = (1.0 - 0.90) * PR * Emfac

      = 0.10 * 54,100 tons/yr. * 3 lb. Cd/ton * ton/2,000 lbs

      = 8.1 tons/yr.

b. Zinc:

Process Rate = 51,900 tons of zinc were produced in 1981 (CARB, 1985c).

Emfac = 0.01 lb. Cd/ton of zinc produced (Coleman, R., 1979)

Ems = PR * Emfac

= 51,900 ton/yr. * 0.01 lb. Cd/ton * ton/2,000 lbs

= 0.26 ton/yr.

5. Cement Manufacturing:

In 1984, California cement manufacturing plants produced 8,722,000 tons of cement (U.S. DOI, 1985) and emitted approximately 3,030 tons of PM (CARB, 1985d) excluding PM emissions from fuel.

Assuming the cadmium concentration in the cement kiln dust removed from the rotary kiln baghouse or ESP equals the cadmium concentration in the particulate matter, cadmium emissions from cement manufacturing can be estimated from total PM emissions and the Cd concentration in cement kiln dust.

Cadmium concentration in cement kiln dust from 9 California cement plants ranged from 5 ppm to 352 ppm and averaged 79 ppm (Haynes and Cramer, 1982; CARB, 1985e). Using these data and the total PM emission, the 1984 cadmium emissions from California cement plants are estimated to be:

Lower Estimate	Upper Estimate	Estimate based on mean Cd concentration
(TPY)	(TPY)	(TPY)
0.015	1.1	0.24

6. Resource Recovery:

Cooper Engineers, Inc. reported an uncontrolled emission factor of 3.04×10^{-6} lb. Cd per million Btu of solid waste heat content (Cooper Engineers, Inc., 1984). The emission factor was obtained from test results conducted at the Gallatin municipal waste-to-energy facility in Tennessee. It was assumed an overall of 99% controlled by application of fabric filters (CARB, 1984). The controlled emission factor, assuming 99% controlled, is therefore 3.06×10^{-6} lb. Cd per million Btu.

Annual average waste burned at the North County Recycling and Energy Recovery Center is 46.5 tons/hr or 5.21×10^{8} Btu/hr., assuming waste has an energy of 5,600 Btu/lb. (CARB, 1984). If the Center operates 24 hrs/day, 7 days/week and 50 weeks/yr., cadmium emissions from this facility is calculated as follows:

Ems = PR * Emfac

= 5.21×10^{8} Btu/hr. * 8400 hrs/yr. * 3.04×10^{-6} lb/10^{6} Btu

= 13.3 lbs/yr.

7. Fertilizer:

* Superphosphate applied in 1983 = 6,000 tons (Cushman, R., 1984)
* Emission factor = 0.0002 lb. Cd/ton of superphosphate applied.

Ems = (6,000 tons/yr.) (0.0002 lb. Cd/ton)

= 1.2 lbs/yr.

II. MOBILE SOURCES

1. Combustion:

a. Gasoline:

Motor gasoline consumption in 1984 = 1.224×10^{10} gallons (Morgester, J., 1985). An average cadmium content of gasoline is 0.02 mg/l or 1.67×10^{-7} lbs/gal. (Lee et al., 1973). Assuming all cadmium in gasoline is emitted from vehicular exhaust upon combustion, cadmium emissions from gasoline combustion are calculated as follows:

Ems = 1.224×10^{10} gals/yr. * 1.7×10^{-7} lbs/gal. * ton/2,000 lbs. = 1.0 ton/yr.

b. Diesel Fuel:

Diesel fuel consumed in 1983 by California motor vehicles was estimated to be 1.46×10^{9} gallons (CARB, 1983). Cadmium content of diesel fuel is 0.08 g/m^3 or 6.7×10^{-7} lbs/gal. (Tierney, et al., 1979). Based on estimates made in 1983 of consumption of diesel fuel in 1984, and assuming all cadmium in diesel fuel is emitted, cadmium emissions from diesel-powered vehicles are estimated as follows:

Ems = 1.46×10^{9} gal/yr. * 6.7×10^{-7} lb. Cd/gal. * ton/2,000 lbs. = 0.5 ton/yr.

c. Motor Oil:

In 1984, VMT driven by motor vehicles in California were estimated to be 1.67×10^{11} (CARB, 1983). An estimated emission factor of 0.6 gram of cadmium emitted per million kilometers driven, or 2.12 lbs. of cadmium emitted per billion

VMT driven, was reported (Tierney, et al., 1979). Cadmium emissions from this source are estimated as follows:

Ems = 1.67×10^{11} VMT/yr. * 2.12×10^{-9} lb. Cd/VMT

ton/2,000 lbs. = 0.2 ton/yr.

Together, cadmium emissions from combustion of fuel and oil in motor vehicles are estimated as 1.7 tons in 1984.

2. Tire Wear:

For every million kilometers driven, 3 grams of cadmium are emitted (0.11 lb. of cadmium per billion VMT driven) (Tierney, et al., 1979). Cadmium emissions from wear-and tear of vehicle tires are estimated as follows:

Ems = 1.67×10^{11} VMT/yr. * 0.11 10^{-9} lb. Cd/VMT * ton/2,000 lbs.

= 0.9 ton/yr.

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CARB, 1986c. Data retrieved from EDS, Inventory Year 1984, ARREPORT JOB 5951, run date 9-9-86. Emission Inventory Branch, Technical Support Division, Sacramento, CA.

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APPENDIX D

ARB ANALYTICAL METHODS FOR SAMPLING AND ANALYSIS OF ATMOSPHERIC CADMIUM

Method for Sampling and Analysis of Atmospheric Cadmium
Method 109

1. Method

1.1 Ambient air suspended particulate is collected on a glass fiber filter for 24 hours using a high-volume sampler.

1.2 The cadmium in the particulate sample is solubilized by extraction with nitric acid, facilitated by ultrasonication.

1.3 The cadmium content in ambient particulate samples is analyzed by flame atomic absorption spectrometry, using an electrodeless discharge lamp, a wavelength of 228.8 nm, a continuum source background correction, and the optimum instrumental conditions recommended by the manufacturer.

1.4 If the cadmium content of the sample is below the detection limit of the flame atomic absorption spectrophotometer, the heated graphite furnace (flameless AA) is used!

2. Apparatus & Supplies

2.1 The hi-volume sampler used to collect the sampler is described in Appendix D, "Procedure for Use of a High-Volume Sampler" (Air Resources Board Procedures Sampling and Analysis of Atmospheric Toxics).

2.2 Heated ultrasonic water bath.

2.3 Atomic Absorption (AA) Spectrophotometer equipped for automated flame and flameless analyses (graphite furnace, and Cd electrodeless discharge lamp.

2.4 Zero air - for flame analysis.

2.5 Acetylene - for flame analysis.

2.6 Argon - for flameless (graphite furnace) analysis.

2.7 Associated glassware: volumetric flasks, pipettes, 100 mL test tubes, mixing cylinder or centrifuge tubes with caps, funnels (for filtering samples, if desired).

2.8 Polyethylene bottles. For storage of samples.

2.9 Centrifuge - if desired (in lieu of filtration).

3. Reagents

3.1 Concentrated (16 M) HNO_3 ACS reagent grade HNO_3 and commercially available redistilled HNO_3 has been found to have sufficiently low metal concentrations.

3.2 Distilled or deionized water (metal free).

3.3 3 M HNO_3 - Add 182 mL of concentrated HNO_3 to D.I. water in a 1 L volumetric flask. Mix well, cool, and dilute to volume with D.I. water. CAUTION: Nitric acid fumes are toxic. Prepare in a well-ventilated hood.

3.4 1 M HNO_3 - add 60.7 mL of concentrated HNO_3 to D.I. water in a 1 L volumetric flask. Mix well, cool, and dilute to volume with D.I. water.

3.5 Cadmium, 1000 ppm atomic absorption standard - commercially available.

4. Sample Preparation

4.1 The filter on which the sample is collected is prepared for analysis by ultrasonic extraction. Prepare a clean filter (with no sample collected) to serve as the sample filter blank.

4.2 Cut one quarter of the filter sample into pieces of approximately 1 cm. square and place in a 100 mL centrifuge or test tube.

4.3 Add 33.3 mL of 3M HNO_3 using a pre-set calibrated automatic dispensing pipette (the acid should cover the cut filter pieces completely).

4.4 Cap the centrifuge or test tubes loosely to prevent pressure build-up during the ultrasonication.

4.5 Place tubes in a test tube rack.

4.6 Put enough water in a clean ultrasonic bath so that the water level is slightly above the acid level of the tubes in the rack. Heat the water in the bath to around 180°F.

4.7 Set the rack in the ultrasonic bath.

4.8 Ultrasonicate the samples for 50 minutes.

4.9 Remove the tubes from the bath and add 66.7 mL water to each of the tubes.

4.10 Cap tubes loosely and ultrasonicate for another 15 minutes.

4.11 Filter or centrifuge the contents of the tubes. If the tubes are centrifuged, decant the supernatant. Use the filtrate (or supernatant liquid) for analysis.

4.12 The final concentration of nitric acid in the samples is 1 M.

5. Instrument Conditions

5.1 Prepare the instrument for flame or flameless operation (follow manufacturers recommended operating conditions). Set the wavelength of the atomic absorption spectrophotometer at 228.8 nm.

6. Calibration

6.1 Stock standard solution - 1000 ppm cadmium solution. Available commercially as atomic absorption standard.

6.2 Intermediate standard - 100 µg Cd/mL. Prepare by diluting 10 mL of stock standard to 100 mL with 1 M HNO_3.

6.3 Calibration standard - 0.50 µg Cd/mL (for flame). Prepare by diluting 1.0 mL of the intermediate standard to 200 mL with 1 M HNO_3. For flameless AA, prepare a calibration standard of .01 µg Cd/mL.

6.4 Aspirate the reagent blank (1 M HNO_3) to zero the instrument.

6.5 Aspirate the calibration standard to calibrate the instrument.

6.6 Plot the absorbance vs. µg Cd/mL to give the calibration curve if automatic calibration is not available in the instrument. PE 3030 AA calibrates automatically.

7. Sample Analysis

7.1 Aspirate the samples and filter blanks. Record their absorbances.

7.2 Determine the cadmium concentration in µg Cd/mL from the calibration curve (PE 3030 can do this automatically). Subtract the amount of Cd found in the filter blanks from those found in the samples.

7.3 Samples that exceed the linear concentration range should be diluted with 1 M HNO_3 then reanalyzed.

8. Calculations

8.1 Determine from the calibration curve the concentration of Cd found in the samples and blanks in µg/mL. The PE 3030 AA does this automatically

8.2 Calculate the concentration of Cd in the particulate sample as follows:

$$\frac{\mu g\ Cd}{m3} = \frac{\mu g\ Cd^*}{mL} \times 100\ mL\ ^{**} \times \text{diln factor (if any)} \times 4\ ^{***}$$

*µg Cd/mL = (µg CD/mL found in sample -µg Cd/mL found in filter blank)

** final volume of the extract solution

*** if 1/4 of filter is used.

9. Precision and Accuracy

Single laboratory, single operator data were collected for Cd using automated flame atomic absorption technique with background correction. 2 and 5 µg Cd were spiked on 1/4 EPM Whatman 2000 glass fibre filters and extracted according to the procedure given above . Recovery values (7) from several replicates are given below.

$\frac{\mu gm}{ml}$ Cd	# replicates	% Recovery
0.02	6	100 ± 15
0.15	7	100 ± 10

References

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(2) "Standard Operating Procedures for Acid Extraction of Glass-Fiber Filters" EMSL/RTP-SOP-EMP-003, November 1981

(3) Harper, S. L., Walling, J. F, Holland D. M. & Pranger L. S. Anal Chem. 1983, 55, 9, 1554-1557.