SUMMARY REPORT AND COMMENTS

on the review of

Biological Indicators Of Exposure To Cadmium And Lead
Part II
Palmerton, Pennsylvania
Draft For Public Comment
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for:

The Palmerton Citizens For A Clean Environment

In Response To Task Schedule #8

AUTHORIZATION

The following report has been prepared in response to a request from the Palmerton Citizens for a Clean Environment (PCCE) for a review of the above-referenced document, in accordance with Task Schedule #8, issued May 10, 1994. The observations and conclusions contained herein are those of the MKA Project Team.

Task Schedule #8 requests that the MKA Project Team perform the following three tasks:

1. Review and comment on Part II of the ATSDR Health Study.

2. Address the following:

   -How significant are the limitations of the studies, ie. occupational exposures applicable to residential situations, etc.?

   -Superfund is a risk based program, what, if any influence should the health study have on the cleanup of Operable Unit #3?

3. Time frame for Task Schedule #8:

   -May 31, 1994, be prepared to give a concise oral presentation to the PCCE Board. This should include a brief reiteration of your written comments on Part I of the Health Study and your current report. Together with your comments on Part II, this will bring us up to date. We're hoping your presentation will be approximately 20 minutes in length.

   -June 9, 1994 will be PCCE's general membership meeting with a public presentation of Parts I and II of the Health Study, again about 20 minutes in length. EPA has been invited to attend and time must be allocated to them. This presentation must be in lay terms.

   -June 18, 1994, written summary report to be submitted to the ATSDR prior to the June 18th deadline for the public comment period.

REVIEW OF THE ATSDR PART II HEALTH STUDY

BACKGROUND

The Biological Indicators of Exposure to Cadmium and Lead, Palmerton Pennsylvania, Part II, draft for public comment, dated April 1994 was prepared by the U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry (ATSDR), as technical assistance to the Pennsylvania Department of Health. It is significant that the ATSDR has maintained an active interest in Operable Unit #3 of the Palmerton Zinc Superfund Site for at least the last 7 years, beginning with the issuance of a Health Assessment Memorandum on February 4, 1987. In addition, an analogous office of the same agency, the U.S. Department of Health, Center for Disease Control, has conducted epidemiological studies in Palmerton since at least 1975.

During August and September of 1991, the ATSDR conducted sampling of blood and urine specimens for lead and cadmium analysis in the neighboring communities of Jim Thorpe and Palmerton, Pennsylvania as part of a comparative health study. Concurrent with the ATSDR study, EPA conducted sampling of environmental media, including interior and exterior paint, soil, dust, and tap water to determine concentrations of arsenic, cadmium, lead and zinc. The results of these two studies were compared and subjected to a series of statistical analyses, as reported in the April 1993 draft ATSDR publication titled: Biological Indicators of Exposure to Cadmium and Lead, **Part I**, Palmerton, Pennsylvania. A Summary Report and Comments on the ATSDR Part I Biological Indicators study was completed by the MKA project team on June 24, 1993, in response to PCCE Task Schedule #6.

In addition to the blood lead and urine cadmium analysis, as reported by the Part I study referenced above, the ATSDR also performed a panel of medical tests to evaluate immune system, kidney, blood, and liver functions in study participants. The results of these analyses were reported in the April 1994 draft ATSDR publication titled: Biological Indicators of Exposure to Cadmium and Lead, **Part II**, Palmerton, Pennsylvania, which is the subject of this review.

Other significant ATSDR contributions towards an understanding of potential health risks related to the Palmerton Zinc Superfund Site include, but are not limited to: a community meeting at the Palmerton High School cafeteria on September 29, 1992, to publicly address the preliminary results of the Part I ATSDR health study mentioned above; and issuance of a Health Consultation for the Palmerton Zinc Superfund Site to Charles Walters, ATSDR Senior Regional Representative, EPA Region III (The ATSDR Health Consultation was reviewed by the MKA Project Team in accordance with PCCE Task Schedule #7). Consequently, it can be established that the ATSDR has sufficient knowledge and experience with Operable Unit #3 of the Palmerton Zinc Superfund Site, to be regarded as the definitive authority on issues related to the potential for risks to human health, due to environmental contamination of the Palmerton area.

The ATSDR Biological Indicators of Exposure to Cadmium and Lead, Palmerton, Pennsylvania, Part II, which serves as the subject of this review, is a Draft for Public Comment. The report is organized into fourteen primary sections: Disclaimer, Abstract, Introduction, Objectives, Methods, Results, Discussion, Conclusions, Recommendations, Authors, Acknowledgements, References, Tables, and Appendices. Because the intent of this review is to provide an interpretive and educational overview that can be applied towards the submission of formal comments to the ATSDR, it will focus only on those sections that are summary in nature, most relevant to the community at large, and therefore of greatest interest to the PCCE (i.e. the Abstract, Introduction, Objectives, Methods, Results, Discussion, and Conclusions).

ABSTRACT

The Abstract provides appropriate background information by identifying the authority under which the ATSDR conducted it's investigation (as assistance to the Pennsylvania Department of Health); and briefly outlines the design and objectives of the Part I and Part II studies. The stated objective of the Pennsylvania Department of Health (PADOH), through technical assistance from the ATSDR, is to **"...determine whether residents in the target area of Palmerton had been exposed to excess amounts of cadmium and lead."**

After providing a very brief overview of the design and methodology of the two studies, the abstract makes the following conclusive statements:

* " No difference was found between study participants living in the two areas in measure of organ system disfunction."

* "For the total study population, regardless of which community they lived in, urine cadmium levels were correlated with some measure of renal dysfunction."

* "Heavy metal exposure levels in the participants of this study (urine cadmium <2.2 micrograms per gram creatinine, blood lead <25 micrograms per deciliter) might have been too low to cause detectable organ system changes."

* "Alternatively, the set of biomarkers of organ system disfunction used in this study might not have been sufficiently sensitive to potential subclinical changes caused by low levels of heavy metal exposure."

* "Continued research into markers of subclinical organ system disfunction is needed to enhance the ability of early detection and disease prevention."

INTRODUCTION

The Introduction identifies the primary route of environmental contamination as airborne emissions from smelting operations resulting in elevated levels of zinc, cadmium, and lead. A brief description of the status of current operations (i.e. demolition of the west plant, and electric arc furnace dust recycling at the east plant) is also provided. The Introduction also states: "The Pennsylvania Department of Health (PADOH) requested technical assistance from the Agency for Toxic Substances and Disease Registry (ATSDR) to determine whether the environmental contamination resulting from the site, represented a public health hazard for the residents of Palmerton."

OBJECTIVES

The ATSDR Part II report states the following **Objectives**:

1. To characterize the distribution of selected biomedical test values, which indicate clinical and subclinical organ system disfunction, in the target population and compare them with the distribution of biomedical test values in the comparison population.

2. To compare the distributions of the medical test values in the target and comparison populations with standard reference ranges for these tests.

3. To determine the extent to which internal dose measurements of lead and cadmium in blood and urine are associated with the distribution of biomedical test values.

METHODS

The Methods section primarily describes the general study design and the statistical analyses used to interpret the biomedical test data. In general, the Part I and Part II studies were designed to provide a comparison of biological indicators of exposure to cadmium and lead (by measuring blood lead and urine cadmium) and to assess the functional performance of four organ systems (blood, liver, immune, and kidney) from a cross section of the target community (represented by the Boroughs of Palmerton and Aquashicola) and the comparison community (represented by the central area of East Jim Thorpe). Three age groups of study participants were assessed:

* Children from 6 to 71 months old;
* children from 6 to 14 years old; and,
* adolescents and adults from 15 to 75 years old.

In addition to providing blood and urine samples, participants were asked to complete a standardized questionnaire that requested information about demographics, tobacco and alcohol use, recent illnesses and disease, and other factors associated either with exposure to cadmium and lead or to findings of the medical test battery.

With respect to meeting the second objective of the Part II study, the General Study Design discussion of the **Methods** section states: **"Specialized tests in the immune panel and renal panel do not have standardized reference ranges covering the age ranges included in this study."**

The remainder of the **Methods** section describes how the data was transformed to provide meaningful results, and the different types of statistical analyses used to interpret the data. For Example: data transformation was required for urine cadmium, urine albumin, and urine beta-2-microglobulin to compensate for differences in urine creatinine levels between men and women, and between different age groups.

The statistical analyses of the results were conducted in three phases:

1. The distribution (statistical measures of range and frequency) of each variable (biomedical test result) was characterized for the target and comparison communities.

2. Each variable was compared independently for the target and comparison communities, within the three age groups - separately and combined - to determine whether there was a significant difference between the two communities.

3. Linear regression models were constructed to evaluate the association between the biomarker values and variables representing exposure (either living in the target or comparison communities, or levels of urine cadmium or blood lead), while simultaneously controlling the effects of multiple confounders.

This resulted in three levels of analysis:

1. Univariate analysis generated descriptive statistics. Means, standard deviations, and ranges were used to describe continuous variables. Frequencies, and percentiles were used to characterize the distributions of categorical and ordinal variables.

2. Bivariate analysis was used to provide a crude measure of association between outcome measures and exposure measures. Examples of bivariate analysis used for this study include: the Kolmogorov-Smirnov (KS) test, the two sample student's t-test, odd ratios (OR's), correlation coefficients between two continuous variables, and simple linear regression.

3. Multivariate linear regression models were run to control for potential confounders. For each dependent variable, a set of control factors was selected based upon a priori interests, such as age, sex, smoking, or alcohol consumption, etc. Separate models were run substituting either area of residence (target versus comparison area), creatinine-adjusted urine cadmium, or blood lead as the independent variable of interest.

The **Methods** section concluded with the following statement. **"Because of the number of statistical tests performed, some statistical associations were expected due to chance alone. The reader is cautioned not to put too much emphasis on any one finding."**

RESULTS

The **Results** section provides a more detailed description of the specific organ system indices used to determine whether residents in the target area of Palmerton had been exposed to excess amounts of cadmium and lead.

The following is a brief summary of findings related to Exposure Levels:

1. As expected, blood lead levels were highest for young children less than 6 years of age.

2. Also as expected, urine cadmium measures were highest for adults and lowest for young children, reflecting the cumulative nature of cadmium exposure and excretion.

3. Factors found to be predictive of blood lead in children included demographics, housing, and behavior.

4. Factors found to be predictive of blood lead in adults include demographics and smoking.

5. Factors found to be predictive of cadmium levels in children include age and sex.

6. Factors found to be predictive of cadmium levels in adults include age, sex, smelter work, hobbies, and cigarette smoking.

Specific indices of blood system function that were evaluated include: Hematocrit, Hemoglobin, Mean Corpuscular Volume (MCV), and Mean Corpuscular Hemoglobin (MCH). The association between measures of blood system function and blood lead was of special interest given the known association between high blood lead levels and blood system effects. The results of the blood system analysis are as follows:

1. There were no statistically significant differences ($p<0.05$) in the percentage of participants from the two areas with blood system values outside the normal range for any of the four indices.

2. Palmerton area children within the 6 to 71 month age group had slightly higher hematocrit values, and Palmerton area children within the 6 to 14 year age group had slightly higher geometric mean MCV values than children from the East Jim Thorpe area. However, these tests did not take into account age or sex differences between the two populations that could have accounted for the observed statistical differences.

3. When the effect of area of residence was examined in multivariable models controlling for age and sex (and pack years of cigarette smoking, and drink years of alcohol consumption for the adult age group), area of residence was not predictive of any of the four blood indices for any age group.

4. Blood lead was not predictive of any of the blood system indices in the two age groups of children when age and sex were simultaneously controlled for in the multivariable linear models.

5. For adults, creatinine adjusted urine cadmium levels were found to have a statistically significant relationship to higher hematocrit and hemoglobin levels, however this relationship was determined to be biologically insignificant. No relationship was found for MCV or MCH in adults, or for any of the indices among children.

Specific indices of liver system function that were evaluated include: alanine aminotransferase (ALT or SGPT), aspartate aminotransferase (AST or SGOT), gamma glutamyltransferase (GGT), and total protein. The biochemistry of these indices is beyond the scope of this review, however it can be generalized that they are amino acid enzymes used to measure metabolic functions related to energy production and protein synthesis. The results of the liver system analysis are as follows:

1. Statistically significant differences were identified for GGT and total protein when all ages were combined, however this finding might have been due to the different sample sizes of the different age groups for each study area.

2. When the effect of area of residence was examined in multivariable models controlling for age and sex (and pack years of cigarette smoking, and drink years of alcohol consumption for the adult age group), area of residence was not predictive of any of the four liver function indices for any age group.

3. Elevated blood lead or urine cadmium levels were not associated with having a liver index level in the upper 5 percentile of adults.

4. Neither Blood lead nor creatinine adjusted urine cadmium was predictive of any of the four markers of liver function for any of the three age groups when assessed in multiple linear regression models.

Two characteristics of the immune system were evaluated during the ATSDR Part II study: Immunoglobin Levels and Lymphocyte Phenotypes. The results of the immune system studies are as follows:

Immunoglobin levels

The levels of the following three immunoglobins were evaluated: IgA, IgG, and IgM. The results of the immune system evaluation are as follows:

1. The statistical analysis indicates that children from the Palmerton area have a lower mean IgM level than children from East Jim Thorpe.

2. Having an elevated blood lead or urine cadmium level was not associated with having an immunoglobin level in the lower 5 percentile of adults.

3. Blood lead was not predictive of any immunoglobin level using simple linear regression.

4. Neither area of residence, blood lead level, nor urine cadmium level was predictive of any of the immunoglobins for any of the three age groups when assessed in multivariable linear regression models.

Lymphocyte Phenotypes

1. No statistically significant difference was found between residents in the Palmerton area and residents of East Jim Thorpe for any age group in the distribution of the lymphocyte panel.

2. Having an elevated blood lead or elevated urine cadmium was not associated with having a lymphocyte phenotype index level in the lower 5 percentile of adults.

3. There was no association between having a blood lead level greater than or equal to 10 ug/dL and any of the lymphocyte tests in any age group.

4. None of the selected independent factors (area of residence, creatinine-adjusted urine cadmium, and blood lead) was associated with the lymphocyte biomarkers and the models themselves were generally poor, explaining less than 22% of the variability of the data.

Kidney function indicators included the following parameters: Serum Creatinine, Blood Urea Nitrogen (BUN), Renal Enzymes (alanine aminopeptidase, gamma glutamyltransferase, and N-B-acetylglucosamine), and Renal Proteins. The following is a summary of results related to kidney function indices:

1. No difference between the two study areas was found in the proportion of serum creatinine or BUN outside of the standard reference range.

2. Having an elevated blood lead or urine cadmium level was not associated with having BUN or creatinine above the standard reference range in adults.

3. Area of residence was not associated with either BUN or Serum Creatinine levels, among any of the age groups, even when controlling for potential confounders such as age, sex, diabetes, alcohol consumption, or cigarette smoking in multivariable models.

4. The distributions of urine renal enzymes were similar for both communities.

5. Having an elevated blood lead level was not associated with having an elevated urine renal enzyme level.

6. When multivariable models were used, area of residence was not statistically significant for any of the three enzymes for any of the age groups examined. Analysis conducted in Part I of the ATSDR Biological Indicators study showed that target area adults 40 through 75 years of age had statistically significantly higher urine cadmium levels than the same aged adults living in the comparison area. When biomarkers of renal dysfunction were examined (using multivariate linear regression models) for individuals in the 40 to 75 year old age group, no significant differences were found between the two communities. The apparent difference in exposure levels did not correspond to a difference in these markers of renal system disfunction.

7. Among adults aged 15 through 75 years, cadmium was a statistically significant or borderline predictor of AAP ($p=0.051$) and NAG ($p=0.011$).

8. Having an elevated blood lead or urine cadmium level was not associated with having a protein value in the upper 95 percentile among adults.

9. Area of residence was not significant for any renal proteins when assessed in multivariable models.

DISCUSSION

The **Discussion** section provided an overview of the strengths and limitations of the study. In addition, an interpretation of various factors that may have effected the results of the biomedical test batteries for each organ system studied is also provided.

The study had several limitations, including:

1. Many of the tests have had limited use outside occupational settings to assess organ-system dysfunction related to chronic low level lead and cadmium exposure. Consequently, reference ranges have not been well established, especially for children.

2. Reliable interpretation of the type of biomedical tests used in this study would require a thorough evaluation of many confounding variables, all of which might not be known.

3. Although reference ranges for some tests of organ system functions evaluated in this study are well established, the sensitivity, specificity, and predictive value for many of these tests have not been established for specific contaminants.

4. There is no reliable method to account for individual variation of test results which might simply be due to biological individuality within populations.

5. Because many of the tests were relatively new in their use for environmental health studies, potential confounders and predictors were largely unknown.

6. Many of the linear regression models poorly described the data. The best model achieved an adjusted R^2 of 0.40, indicating that at best, more than half of the variability was unaccounted for by the independent variables in the multivariable linear regression models.

7. A large number of statistical tests were performed during the course of this analysis, including approximately 220 multiple linear regression models. Some findings of statistical significance would be expected due to chance alone, and therefore, caution should be taken not to place too much emphasis on any one statistically significant finding. Further, some statistically significant findings were not biologically significant.

The study also had several strengths, including:

1. The study used a comprehensive battery of tests to assess blood, liver, immune, and kidney functions. Some of the kidney function tests are considered to be the most sensitive for early organ system disfunction.

2. The inclusion of biomarkers of exposure (blood lead and urine cadmium) provided an opportunity to examine the effect of exposure on the organ systems considered to be the most sensitive targets for these metals.

3. The inclusion of biomarkers of exposure also removed the need for using proxy measures of exposure, such as job classification or the distance of the home from the exposure source.

4. The use of biomarkers of organ system dysfunction provided objective measures of health status rather than relying solely upon self-reported symptoms and illnesses.

Several prominent statements made in the interpretation section of the **Discussion** including:

1. No difference was found in the measures of organ system disfunction between the target and comparison areas. This lack of difference was not unexpected since cadmium and lead exposure levels were relatively low in comparison to occupational settings. Further, participants from the two study areas had generally similar blood lead and urine cadmium levels, although older target area adults had higher urine cadmium levels than comparison area adults. Demographic factors which might be related to health status were also similar between the two communities.

2. Blood system biomarkers such as hematocrit, hemoglobin, MCV, or MCH did not correlate statistically with area of residence, urine cadmium, or blood lead levels. This may be because the selected biomedical tests used are not sensitive enough to detect effects from relatively low blood lead levels (<25ug/dL).

3. Immune system functions did not correlate with area of residence, blood lead levels, or creatinine-adjusted urine cadmium. Once again, this may be because there is no measurable effect to the immune system at blood lead levels <25ug/dL, or the immune markers might not be sensitive to immune system dysfunction at these blood lead levels.

4. Area of residence, urine cadmium, and blood lead levels were not found to effect liver system biomarkers. This suggests that there is no indication of organ system toxicity, which may be due to the generally low contaminant levels measured in this study. However, there is little supporting evidence for liver disfunction in chronically exposed human populations. More sensitive biomarkers may be needed to detect preclinical changes in the system.

CONCLUSIONS

The ATSDR Part II report states the following **Conclusions**:

1. There was no difference between the Palmerton area sample population and the East Jim Thorpe area sample population in the distribution of markers of kidney disfunction, liver disfunction, immune disfunction, or blood system disfunction. Although it was determined in the Part I study that Palmerton area residents, 40 to 75 years of age, have higher urine cadmium levels than East Jim Thorpe area residents in the same age group, no difference in kidney function was found between those sample populations.

2. For the total population, regardless of town, cadmium exposure, as measured using creatinine-adjusted urine cadmium, may affect the renal system as measured by AAP and NAG. Further research in needed to confirm whether renal impairment occurs in association with chronic, low-level environmental cadmium exposure (2ug/g).

3. Blood lead was not found to be associated with any of the biomarkers examined.

COMMENTS ON THE ATSDR PART II STUDY

1. A significant level of effort was expended to conduct this study. In general, the investigation is well-documented and the objectives and conclusions are well-focused and clearly delineated. The statistical analyses of the data seem to be appropriate; the authors made considerable efforts at exploiting the data for potential relationships that might provide insight to monitoring of environmental health concerns of exposure to lead and cadmium.

2. Another asset of the study was the use of a range of biomarkers encompassing four different organ systems. While some documented (e.g., peer-reviewed literature) rationale for the selection of these parameters might have been made in the introduction or methods sections, generally, this seemed evident from the discussion section and its respective literature citations.

3. The authors are explicit in recognizing and documenting both the limitations and strengths of the study. Furthermore, they are appropriately conservative in their interpretation of their findings, and they explicitly recommend caution to avoid placing too much emphasis on any one statistically significant finding, especially in light of the large number of statistical tests performed and the very few statistically significant relationships actually found.

4. Given the current problems and limitations in this area of environmental health research (e.g., few studies have been conducted on nonoccupationally exposed people or among children), the study does make contributions to the advancement of the field. However, these contributions are general in nature (and well-documented in their "study strengths" section) and are difficult to apply for specific applications to Palmerton (or Jim Thorpe).

5. In general, interpretation of the data, and the conclusions stated in the report appear to be well founded. The proper cautions are well indicated in the study, taken as a whole within the context of a technical document. However, it will be very easy to misrepresent the findings and conclusions of the study, especially with short quotations taken out of context in the popular press.

6. In particular, there is a strong potential for misrepresentation of the first conclusion (p. 18), that there is no difference between target and comparison areas regarding biomarkers for the four organ systems. This is well supported by the analyses, but it should not imply that there are no environmental health concerns at Palmerton (note that this report does not imply this). Within the overall report, it is evident that these biomarkers were developed for occupational exposures and they may not be sensitive enough to detect effects at lower nonoccupational levels typical of Palmerton and Jim Thorpe; this condition is explicitly stated several places in the report on pages 15-16. This situation, plus the fact that there were very few statistically significant relationships, severely limits the use of these biomarkers as a risk assessment tool for specific concerns at Palmerton (or Jim Thorpe).

7. The real advantage of this study is for the general field of monitoring of public health using biomarkers (and not for specific assessments or remedial actions at Palmerton or Jim Thorpe). As stated before, this is well-documented in the study strengths sections of the report. Again, the authors clearly recommend that additional research is needed to enhance the ability of early detection and disease prevention; they state on pages 15 and 16 that it is uncertain as to whether these biomarkers (except for the renal system as measured by AAP and NAG) are sufficiently sensitive to detect health effects in a nonoccupational environment. Therefore, one should not jump to the conclusion that there are no health concerns at Palmerton just because there were no statistically significant differences between the target and comparison areas for these particular biomarkers, used almost exclusively in occupational settings.

8. On the basis of comments provided in points 5, 6, and 7 above, the study might list one additional conclusion, specifically in the Conclusions Section: that, in general, very few statistically significant relationships were found (only 15 were reported in the text while 27 might have been expected due to chance alone [i.e. 5% of 550 different tests performed at the 95% confidence level]); therefore, the biomarkers selected (except for the renal system as measured by AAP and NAG) may not reflect adequately the level of metals exposure expected in a nonoccupational environment like that at Palmerton or Jim Thorpe.

9. In summary, this study (ATSDR Biol. Indicators...Part II) should not be used to make any assessments of risk at Palmerton in particular; the report does not try to do this but as indicated above, the conclusions could be misinterpreted in the general press. Therefore, it is recommend that the ATSDR Health Consultation (Palmerton, Zinc...; April 12, 1993) report be used as the basic reference for risk assessment at Palmerton (in conjunction with other standard references like EPA's Risk Assessment Guidance for Superfund manual).

10. Because there were few statistically significant findings in this study, it is not necessary to overemphasize some of the more serious concerns related to study design (e.g. relatively high levels of lead at Jim Thorpe, the comparison site, and the lack of discussing this in a broader context) that were addressed in our review of the Part I report. However, it should be kept in mind that these are still issues that need to be addressed within the context of an objective scientific investigation, especially when it concerns the health and welfare of an entire community.

11. In terms of the study design, it is important to reinforce to the lay person that many of the conclusions reached in the Part I study, some of which were carried over as assumptions applied to the Part II study, were based upon correlations, which are very useful for identifying relationships, but have limited application when it comes to establishing causality. This is reinforced in the Discussion of Study Limitations on page 14 of the Part II report, where it is stated that some statistically significant findings were not biologically significant.