DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

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Mark Jacobs, MD
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Dear Dr. Jacobs:

As requested by the Ministry of Health of New Zealand, I have reviewed the following documents prepared by the Institute of Environmental Science and Research Ltd (ESR): *A Study of 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) Exposures in Paritutu, New Zealand,* the final report dated February 2005 and the interim report dated August 2004. I was also provided and examined the raw data for the Paritutu participants used in the ESR analysis. I also read each of the accompanying appendices A-O. As I am not an expert in environmental assessment or laboratory analysis of serum PCDDs, PCDFs or PCBs, I did not think it appropriate for me to provide comments. It was apparent from the list of scientific reviewers that these components of the study were examined by international experts in the field and, thus, gave me confidence that the generated data and results were of significantly high quality.

I am very pleased to have been given the opportunity to work with the staff of the Ministry of Health during the process of the review. To a person, they were extremely helpful throughout.

I have not received monetary or in kind compensation from the Ministry of Health for this activity because it relates to the work that I have done as an employee of the United States Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health. Furthermore, the findings and conclusions of this review have not been formally disseminated by the National Institute for Occupational Safety and Health and should not be construed to represent any agency determination or policy.

In summary, I found that the study met its overall objectives and was comprehensive in its approach to assessing the range of serum 2,3,7,8-tetrachlorodibenzo-p-dioxin concentrations in the residents of Paritutu, potential routes of exposure and modes contamination. My specific comments are included in the attachment.

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The Ministry of Health asked that I consider the following questions:

1. Does the ESR Report fulfill its objective?
2. Is the ESR methodology and analysis sound?
3. Does the Leonard review affect the findings and recommendations identified in the ESR report?
4. If the Leonard review does affect the findings and recommendations to what extent and how material is this?
5. Any other comments and observations you feel may be relevant, for example you may wish to comment on the methodology of the study more broadly.

1. Does the ESR Report fulfill its objective?

The report states that "the purpose of the study was to assess only the potential exposures to dioxins in the community through measuring blood levels of dioxins."

The report appears to have fulfilled the objective of its mandate as stated in the ESR report. The study evaluated not only serum 2,3,7,8-TCDD concentrations among a sample of Paritutu residents with a high likelihood of exposure, but also thoroughly evaluated and estimated all known potential sources of current (dietary) and recent past exposure to 2,3,7,8-TCDD (airborne). It is impressive to learn that the research team used all the available current technology to measure and model potential exposures to determine which segment of the population may have had the highest exposures.

Although the sample size of people for whom serum 2,3,7,8-TCDD concentrations were determined is small, I am not sure that there would be sufficient gain in analyzing additional serum samples, despite the fact that the calculated confidence limits might be more stable with larger numbers. Small sample size notwithstanding, the study data illustrate the likely range of current serum 2,3,7,8-TCDD concentrations in the Paritutu populations. Furthermore, the calculation of half-life extrapolated concentrations is the best estimate of peak serum 2,3,7,8-TCDD concentrations which most likely occurred during 2,4,5-T production. The authors also recognized the variability in the published adult half-life for 2,3,7,8-TCDD, thus used a range of values to calculate possible upper and lower limits of the estimated 2,3,7,8-TCDD peak serum concentration.

The report confirms that some residents of Paritutu were exposed to presumably high airborne concentrations of 2,3,7,8-TCDD sometime between 1962 and 1987, and that they continue to have above background serum 2,3,7,8-TCDD concentrations. The assumption that duration of residency and age are related to serum 2,3,7,8-TCDD concentrations is very plausible, although length of residency and age are probably highly correlated if the individuals remained within the exposure area for most of their lives. This does not negate the findings but should be taken into consideration in the analyses. It is also possible that the dynamics of uptake and elimination might differ among individuals who were resident in Paritutu for varying periods during 2,4,5-T

production and post-production years, but that is hard to determine from this study, and not the objective. Furthermore, distance of residence from the plant or location of the residence within the plume might also contribute to the potential for exposure, but I did not see the results of these analyses.

The complete data set, including the environmental modeling and data obtained from the Paritutu populations, should provide governing bodies sufficient information to develop and implement informed policies on remediation, public health guidance and other actions suitable for the region.

2. Is the ESR methodology and analysis sound?

With respect to the development of the plan and criteria for selection of study participants, the solicitation of study participants and the statistical analyses of serum 2,3,7,8-TCDD concentrations, the methodology is sound. In addition, the research team went to great lengths to identify a highly qualified, internationally recognized laboratory to analyze the serum samples.

I have no objections to the research team combining data from Parts I and II of the study. Part II, a supplement to Part I, permitted the authors to 1) better determine the range of serum 2,3,7,8-TCDD concentrations in the population, 2) more robustly evaluate the relationship between length of residence in Paritutu, age and 2,3,7,8-TCDD concentrations, and 3) increase the study sample size.

While I am neither an environmental chemist nor an expert in fate and transport of 2, 3, 7,8-TCDD in the environment, the approach to assessing dispersion and deposition in the environment are consistent with what others have done. The study also appears to have undergone a comprehensive review by many of the scientists with the greatest experience in the field. I assume that the authors have addressed their input where appropriate.

3. Does the Leonard review affect the findings and recommendations identified in the ESR report?

Dr. Leonard points out relevant issues in the 2004 and 2005 reports. As noted below, I reviewed all of Dr. Leonard's comments and added my own thoughts and comments. Dr. Leonard's review is thoughtful and indicative of an intelligent individual who is accustomed to examining data but not necessarily epidemiologic or environmental data. He raises good points that ESR should consider and correct or clarify where appropriate. Seriously considering Dr. Leonard's comments will make the report read better and may help better illustrate the data for policy makers, but they most likely will not affect the analytic approach or the findings of the report

Comments on Dr. Leonard's review.

7.Small Sample Size
7.1-7.9 I agree with Dr. Leonard that the larger the sample the narrower the confidence limits and the better the accuracy of the estimate. He also correctly indicates that there are many variables that might affect the serum concentrations. While I agree that a larger sample size would have been nice, the purpose of the study was to assess the potential exposures of the Paritutu population by measuring serum 2,3,7,8-TCDD concentrations. Granted the individuals selected may not have included individuals with the highest or lowest concentrations within the selected age groups, the data collected provide a plausible range of concentrations in the nonoccupationally exposed Paritutu population. Furthermore, the overwhelming preponderance of 2,3,7,8-TCDD in the TEQ calculation would assert that the source of the 2,3,7,8-TCDD exposure in Paritutu residents was the IWD plant. Therefore, I agree with the Ministry's decision for Part II of the study to limit serum analysis to dioxins and furans but not dioxin-like PCBs.

I am not privy to the funding levels for this study but I am aware that analysis of serum dioxin, furans and PCBs is approximately USD$ 2000 per sample, thus a larger sample might have been financially impossible, thus, the careful and scientifically logical selection of a study population was necessary. The method used for determining the study participants was well designed and executed.

It also should be clearly noted that the serum 2,3,7,8-TCDD concentrations provide only a small part of the total picture of past exposure and should be examined within the context of the larger study conducted by ESR. This includes the TEQ evaluation, the estimation of peak concentrations by using an estimated half-life, self-reports of consumption of homegrown vegetables and poultry and poultry products and a comprehensive environmental analyses.

Thus, I am not concerned by the small number of serum 2,3,7,8-TCDD concentrations.

8. Mixing of data
8.1 -8.4

Tables 2 and 3 of the 2005 report are relevant and should remain in the text. It is important to understand that the two groups are relatively similar and can be combined in the final analysis.

8.5-8.11: Dr. Leonard reorganized the data to evaluate pre and post 1974 exposure. He noted that those with potential for exposure before 1974 have higher serum 2,3,7,8-TCDD concentrations than those expose post 1974. Given the history of the IWD, this is a good illustration of when the heaviest exposures were likely to occur.

I would assume that during the development of the logistic models, estimated length of exposure and duration of residency were added to models as continuous or discrete variables. Did a model evaluate exposure as a dichotomous variable - pre and post 1974?

9. Role of Timing of Residence

9.1 -9.11 I believe that based on Dr. Leonard's comments, there may be some need to further illustrate the data on duration of residency – but without compromising the confidentiality of the study participants. I understand that the linear regression model showed age and length of residence as the only variables associated with serum TCDD concentrations. Can you put the model in the report? What is the correlation coefficient for the relationship between age and duration of residency?

It would be good to add an illustration of the relationship between the serum 2,3,7,8-TCDD concentrations and year – not the total number of years but the actual period of residency in the exposed area. For example, what is the mean concentration of people who lived in the area 1962-1974 rather than the entire period? These may be the individuals with the highest potential for exposure.

Is there anything in the environmental reports and history of emissions from the plant that can be used to inform this analysis?

10. Comparable Data
10.1 – 10.2. I like the estimation of the decrease in concentrations from 1997 – 2004. This is logical and answers Dr. Leonard's concern.

10.3 I am not sure what this comment is about.

11. Conflicting Conclusions
11.1 – 11.3

I strongly recommend that the MOH make statements in the summary and the report consistent. Do not paraphrase the text. Take the wording verbatim from the text to develop the executive summary.

What other studies have found eating of 'exposed' produce to increase serum 2,3,7,8-TCDD concentrations? It might be worth citing other studies that could measure such increases; maybe animal studies? How much would consumption of contaminated vegetables contribute to overall exposure when respiration would be a more likely route of exposure? A very brief discussion of what is currently known about plant uptake of dioxin might be of use to the reader.

11.4-11.10 I agree with Dr. Leonard; the issue of consumption of poultry and eggs is probably a weak issue. But what do other studies find? Again, make sure the statements are defensible and that the summary accurately reflects the text.

I, too, wondered about local fish consumption. It would be worth describing for the reader if the catch is from the sea or from a fresh water source that could have been contaminated from effluent from the plant. I would surmise that fish from the sea would be less likely to be heavily contaminated. But fish caught from a pond where TCDD- contaminated soil could deposit in the sediment, might expose populations eating such fish. There is considerable information in the literature about this topic which could be referenced. However, there is little discussion in the report and the appendices relative to this potential for exposure.

Sections 12 and Inconsistencies and Missing Statistic
The report needs to be looked at by a good editor who is accustomed to reading and editing scientific papers. Many of Dr. Leonard's questions could be resolved by ensuring that the writing is more consistent and that the tables and text match.

Section 21

I would take a look at Dr. Leonard's concern relating pre and post 1974. It would be useful to carefully revisit his issues – perhaps by phone.

21.6. Exposure by breastfeeding.
While this is a possibility, it is not possible to determine which of those who provided serum samples were breastfed. However, I am not aware of studies that looked at serial serum 2,3,7,8-TCDD concentrations among babies breastfed by exposed mothers. It is known that children eliminate dioxins faster than adults given the higher metabolism. A short discussion of this issue might be worth while.

22. Historic levels of TCDD
It would be useful to include a table of the calculated half-lives or some illustration. It would also be illustrative to show the pre1974 exposed vs. post 1974 levels as suggested by Dr. Leonard.

I have a few other questions and comments that arose separate from Dr. Leonard's review. They are as follows:
1) It would be useful to include a discussion of the limitations of the study, the sample size, and the analytic approaches. Could this study have been done differently and, if so, why was it not attempted?

2) How did the authors handle serum 2,3,7,8-TCDD concentrations in the participants that fell below the limit of detection?

3) I would think that for the general public, the appendices, while illustrating all of the work that went into the activity, are a bit daunting. For the final report, I would try to synopsize the key methods, concepts and results and include them in the report so that the reader understands the intent without having to plow through all of the methodology and data.

4) One of the limitations of the published adult half-life values for 2,3,7,8-TCDD is that they are derived from predominantly male study populations, e.g., Michalek et al. I understand that this information is the best we have, but it should be acknowledged. A discussion of the difference between women and men with regard to issues which may affect 2,3,7,8-TCDD retention would be informative.

5) After reviewing the individual data, it is clear that, in general, serum 2,3,7,8-TCDD concentrations from female and male Paritutu residents in the younger age groups fell within the range of normal (base on the MfE data.) However, that of individuals in the age groups 50+ years for men and 35+ for women was outside the range of the New Zealand normal. Yet, for

each age-gender group of the Paritutu residents, many of the concentrations fall within a small range with some outliers in each age-gender group, which exceed the mean concentration by two or three times. Has there been an assessment of what situation or variables might have caused the increased values among the outliers? See point 6 below.

6) A discussion of some key variables which may contribute to serum 2,3,7,8-TCDD concentrations might be illuminating to some readers. These include: a) possible employment at the plant or the use of pesticides contaminated with 2,3,7,8-TCDD. Although these questions were asked of the residents, recall bias is always an issue. I did not read in the report if responses about past employment at the IWD were verified or a response about pesticide use was probed by the study team. b) Obesity, loss of considerable amounts of weight, breastfeeding. It is thought that each of these factors may contribute to retention, depletion or transfer of lipid bound 2,3,7,8-TCDD. Do the authors know about the body mass index of the study participants – at the time of the study and, if possible, at the time of exposure? Did the women breastfeed? Were the younger participants breastfed by women residing in the exposed area? c) Distance of residence from the plant or location of residence within the plume. It is possible that each of these variables may contribute to current and/or peak serum 2,3,7,8-TCDD concentrations and might be considered variables in the serum 2,3,7,8-TCDD models

7) Although PCB concentrations are close to the normal range, in male Paritutu residents, the concentrations were higher than the normal range. Why is this?