



J. Blondell

12/4/86

Shaughnessy No.: 098301

Date Out of EAB: _____

To:

Product Manager
Registration Division (TS-767)

FRANK DAVIDO

From: ~~Herbert Manning Ph.D., Acting Chief~~
~~Environmental Chemistry Review Section 1~~
Exposure Assessment Branch
Hazard Evaluation Division (TS-769C)

Field monitoring /
special projects

Attached, please find the EAB review of...

Reg./File # : _____

Chemical Name: Aldicarb

Type Product : _____

Product Name : _____

Company Name : _____

Purpose : _____

Action Code: _____

EAB #(s) : 70021

Date Received: _____

TAIS Code: _____

Date Completed: 12/4/86

Total Reviewing Time: 2 hours

Monitoring study requested: _____

Monitoring study voluntarily: _____

Deferrals to: _____ Ecological Effects Branch
_____ Residue Chemistry Branch
_____ Toxicology Branch

SPIC Riv.

REGISTRATION DIVISION DATA REVIEW RECORD
—TO BE USED FOR REVIEW OF STUDIES PPA ONLY—

(RED PROVIDE)
PACK No.:
19105-416
12/10/86

Confidential Business Information—
Does Not Contain National Security Info. (E.O. 12065)

CHEMICAL NAME:
Aldicarb

(RD PROVIDE)
SHAUGHNESSY NO.
098301

Identifying Number	Action Code	Reference Number	Record Number	Study Guideline or Narrative Description	Reg. Std. Review Submission Criteria (SEE BELOW)	Accession Number	(RED/BUD/TSS Complete) Study found to be Acceptable (A)/ Unacceptable (U) for review or reviewer comment
098301	870		193409				

PRODUCT MANAGER (PM) or REVIEW MANAGER (RM) AND NUMBER: *Bannagan* PM/RM TEAM MEMBER AND NUMBER: *65*

DATE RECEIVED (EPA): _____ RD BRANCH CHIEF INITIALS: _____

CHECK APPLICABLE BOX:

Adverse 6(a)(2) Data (405,406) Product Specific Data (Reregistration) (655,656)

Suspect Data (415,416) Generic Data (Reregistration) (660,661)

IRT Data (485,486) Special Review Data (870,871)

NUMBER OF INDIVIDUAL STUDIES SUBMITTED: _____

HAVE ANY OF THE ABOVE STUDIES (in whole or in part) BEEN PREVIOUSLY SUBMITTED FOR REVIEW? (circle: yes or no) If yes, please identify the study(ies):

RELATED ACTIONS: *2 ATTACHED QUESTIONS RE: FURCA'S EPI STUDY*

INSTRUCTIONS: *Please consider the attached questions in your review of the Furca Epi-toxicology study on Aldicarb. (10/12/86 Mr. Dr. Firellita in Berkeley)*

TO BE COMPLETED BY RSERB

DATE SENT TO RED/BUD/TSS: *10-10-86*

PRIORITY NUMBER: _____

PROJECTED RETURN DATE: *12/10/86*

DATE RETURNED TO RD (RED/BUD/TSS PROVIDE): _____

REVIEWS SENT TO:

RED: SIS TB RCB EAB EEB RD: TSS BUD: EAB SSB

TO:	TYPE OF REVIEW	NUMBER OF ACTIONS			FOR DATA SUBMITTED UNDER A REGISTRATION STANDARD: Review Submission Criteria
		Reregistration	Special Review	Other	
	Toxicology				Policy Note #31 1 = data which meet 6(a)(2) or meet 3(c)(2)(B) flagging criteria 2 = data of particular concern 3 = data necessary to determine tiered testing requirements NOTE TO TSS: Return 1 Copy To RSERB
	Ecological Effects				
	Residue Chemistry				
	Exposure Assessment <i>Blondell</i>				
	Product Chemistry				
	Efficacy				
	Precautionary Labeling/Acute Tox.				
	Science Support				
	Economic Analysis				

INCLUDE AN ORIGINAL AND FOUR (4) COPIES OF THIS COMPLETED FORM FOR EACH BRANCH CHECKED FOR REVIEW.

REGISTRATION DIVISION DATA REVIEW RECORD
 --TO BE USED FOR REVIEW OF STUDIES PPA ONLY--

(HED PROVIDE)
 PACK No.:

Confidential Business Information--
 Does Not Contain National Security Info. (E.O. 12065)

(RD PROVIDE)
 SHAUGNESSY NO.
 098301

CHEMICAL NAME:

Aldicarb

Identifying Number	Action Code	Reference Number	Record Number	Study Guideline or Narrative Description	Reg. Std. Review Submission Criteria (SEE BELOW)	Accession Number	(HED/BUD/TSS Complete)
							Study found to be Acceptable (A)/ Unacceptable (U) for review or reviewer comment
098301	870		183409				

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Burgan

PM/RM TEAM MEMBER AND NUMBER:

65

DATE RECEIVED (EPA):

RD BRANCH CHIEF INITIALS:

CHECK APPLICABLE BOX:

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 Suspect Data (415,416) Generic Data (Reregistration) (660,661)
 IBT Data (485,486) Special Review Data (870,871)

NUMBER OF INDIVIDUAL STUDIES SUBMITTED:

HAVE ANY OF THE ABOVE STUDIES (in whole or in part) BEEN PREVIOUSLY SUBMITTED FOR REVIEW? (circle: yes or no) If yes, please identify the study(ies):

2 ATTACHED QUESTIONS RE: Fire's EPI Study

RELATED ACTIONS:

INSTRUCTIONS:

Please consider the attached questions in your review of the Fire's Epi Biology Study on Aldicarb. (10/2/86 Tr. Dr. Firella in lab)

TO BE COMPLETED BY RSEBS

DATE SENT TO HED/BUD/TSS:

10-10-86

PRIORITY NUMBER:

PROJECTED RETURN DATE:

DATE RETURNED TO RD (HED/BUD/TSS PROVIDE):

REVIEWS SENT TO:

HED: SIS TB RCS EAB EEB RD: TSS BUD: EAB SSB

TO:	TYPE OF REVIEW	NUMBER OF ACTIONS			FOR DATA SUBMITTED UNDER A REGISTRATION STANDARD: Review Submission Criteria
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	Precautionary Labeling/Acute Tox.				
	Science Support				
	Economic Analysis				

INCLUDE AN ORIGINAL AND FOUR (4) COPIES OF THIS COMPLETED FORM FOR EACH BRANCH CHECKED FOR REVIEW.



State of Wisconsin \ DEPARTMENT OF HEALTH AND SOCIAL SERVICES



October 2, 1986

DIVISION OF HEALTH
MAIL ADDRESS:
1 WEST WILSON STREET
P.O. BOX 309
MADISON, WISCONSIN 53701-0309

Janet L. Auerbach, Chief
U.S. Environmental Protection Agency
Special Review Branch-TS-767-C
401 M Street, SW
WASHINGTON DC 20460

Dear Jan:

This letter is to update you on the status of the Wisconsin Division of Health and the Centers for Disease Control study of chronic exposure to aldicarb-contaminated groundwater and human immune function. As you know, the study findings have prompted the Wisconsin Division of Health to alter its aldicarb drinking water health advisory. The new health advisory, as of September 8, 1986, states that any resident whose drinking water is contaminated with aldicarb at levels of 1 ppb or greater should refrain from drinking that groundwater and obtain an alternative drinking water source. This action was taken to widen the margin of health safety for Wisconsin residents given the findings from our pilot study and pending further research to support or repudiate the findings.

We have instructed study participants to refrain from drinking their aldicarb-contaminated groundwater. Our intention is to return to central Wisconsin in approximately three months and to repeat the immune function testing. This would provide information as to whether the observed changes in T-cell populations are a transient or persistent phenomenon.

I recently received a letter from the Union Carbide Corporation concerning our study with an attached list of 26 questions and comments (copy enclosed). A full response to all of these questions will require an extensive time commitment by myself and the co-authors. As you will note in your review of this list, many of the questions in the Union Carbide document are merely comments on our experimental design or interpretation rather than questions to which I can respond. We are preparing, however, a full response to the Union Carbide document. Additionally, we look forward to questions from the scientific community once our study has been published.

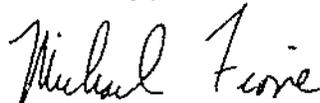
As a pilot epidemiologic study, our research has recognizable limitations. However, the methodology and interpretation of our study did undergo extensive internal review at the Centers for Disease Control. Additionally, the editors and scientific peer reviewers at Environmental Research viewed the work as meaningful and meriting publication in a respected scientific journal. I and the other co-authors continue to stress that these are preliminary findings

Janet L. Auerbach
October 2, 1986
Page 2

from a pilot study. As an epidemiologic investigation, we were able to draw associations, not establish cause and effect. The finding of a statistically significant increase in T8 cells in aldicarb-exposed study participants is a concerning one, not because it implies current, clinically significant disease but, rather, because it may suggest that aldicarb is acting as a modulator on the critically important human immune system. It is for these reasons that the manuscript was written and that the State of Wisconsin has altered its health advisory for aldicarb-contaminated drinking water.

When an appropriate response to the Union Carbide questions is prepared, I will forward a copy of it to you at USEPA. We at the Wisconsin Division of Health and the Centers for Disease Control look forward to working with other government agencies in assessing the importance of our findings. If there is any specific piece of supporting information regarding our study that you would like immediately, please feel free to make such requests. We appreciate your concern.

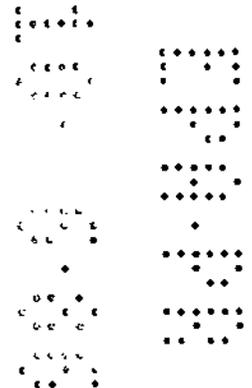
Sincerely,



Michael C. Fiore, M.D.
Centers for Disease Control

Encl.

cc: Lee Thomas
Michael Branagan





From Union Carbide Corp.

10/1/86

DESIGN AND CONDUCT OF THE STUDY

1. According to the information provided, subject participation reported for household well water vs. municipal water was 70% (37 of 53) and 100% (13 of 13), respectively. However, participation by exposure status (presence or absence of aldicarb within the household well water group) was not reported. As such, it is difficult to assess the potential for response bias. To resolve this question, information is needed indicating percent participation by exposure status and any reasons which might account for the difference in subject participation as a function of water source (70 vs. 100%).
2. According to the authors, twenty-seven households did not have an age-eligible female who drank household tap water. How many of these households included age-eligible females? How many of these females had previously stopped drinking household well water? Why were these females not evaluated as part of the study?
3. The study as conducted was limited to female subjects. In addition, the total number of participants (50) is relatively small. Why was the study limited to females? As females are subject to monthly variations including the menstrual cycle, what influence, if any, could these factors exert in a small population size?
4. During the selection of the study participants, was (were) the interview(s) conducted using a structured questionnaire? Were all potential participants asked the same questions and in the same manner? Will copies of the questionnaire be made available to Union Carbide Agricultural Products Company, Inc.?
5. Were the interviews conducted with the interviewers blinded as to the exposure status of respondents? This procedure would be particularly important in making exclusions.
6. Were the study participants aware of the hypothesis under study? It is possible for selective participation to occur as a function of health status. For example, an individual aware of the aldicarb contamination of her drinking water well may have been more likely to participate in the study, especially if recently ill.
7. Do the non-exposed individuals selected for use in this study in fact constitute an appropriate control population? The ultimate selection of 13 of 27 controls from employees of the Portage County Community Human Services Department raises the specter of non-comparability of the two non-exposed populations selected to comprise the control group. Specific differences between the two control groups would include the work environment and dissimilarities between municipal and household well water. The statistical approach to evaluating the comparability of the two component control populations (multiple test of significance) is inadequate due to the limited power to detect differences between the two control groups of only 13 and 14 individuals. The fact that approximately half of the controls arise from a group working in a

DESIGN AND CONDUCT OF THE STUDY, con't

commercial area presents another set of comparability issues with respect to possible confounding variables. It has been well established that the potential confounding of multiple variables should be addressed simultaneously and not by means of multiple tests of significance. As a result of these concerns, it is important to examine the data (Tables 1-4) using the two components of the control population separately. Without a full set of data on all subjects, however, this examination is impossible.

8. The wide variation in the ingestion levels of tap water suggests a very "soft" measure of exposure. Was tap water consumed in food (water used to cook, added to soups, etc.) and hot or cold drinks (coffee, tea) included in the dose assessment?
9. Did the authors make any attempt to determine the length of exposure to aldicarb? For example: how long had an individual lived at the current address?
10. The cross-sectional design of the study does not allow a characterization of time-related effects (i.e., length of exposure to aldicarb), which would strengthen the evidence for causality. For example, did the reported change in T4:T8 ratios predate or occur subsequent to exposure to aldicarb residues in the drinking water? In addition, no personal baseline data are available. Therefore, how can one be certain that the T4:T8 ratios observed are not perfectly normal for those particular individuals? General baseline data from the clinical laboratory are not provided which may also impact these observations.
11. Why were multiple linear regressions or some other regression modeling technique such as logistic regression not utilized in the analyses of the study data? These models permit tests of both the linearity assumption and the existence of a non-zero slope, as opposed to correlation-type analyses which assume a straight line relationship. Why did the authors limit their analyses to include all individuals of the immune function dose-response relationship seen in Table 6? An internal comparison of the immune function findings by levels of exposure among the exposed population only (and appropriate statistical tests for linear trend) would have been more informative. The authors limited their analyses to a univariate approach (i.e., the importance of potential confounders is dismissed based on the lack of a statistical association for each variable treated alone). Furthermore, they equate significant correlations to dose-response relationships. A linear trend between levels of exposure and outcome would be more appropriately tested using multiple linear regression analyses with an independent variable (aldicarb exposure); a dependent variable (immune function), and simultaneous control for age, smoking, socioeconomic status, etc.

DESIGN AND CONDUCT OF THE STUDY, con't

12. Did the correlation analyses include the controls who drank municipal water? If this were the case, then the correlation "dose-response" analyses were not independent of the comparisons between exposed and non-exposed participants and the similar p-values observed in both tests would not be unexpected even where no correlation existed between estimated exposure and effect within the exposed group. It is of interest that the five exposed individuals with decreased T4:T8 ratios (Table 3) had estimated exposure metrics not substantially different from the mean of all exposed individuals (i.e., average aldicarb level 19.2 ppb versus 16.1 ppb for total exposed group and 15.6 ug/day versus 15.0 ug/day for the total exposed group). What correlations are obtained based on a subanalysis of the "exposed" group alone?
13. On a related note, why is the Pearson Correlation Coefficient mentioned in the methods section and the Spearman Rank Correlation Coefficient reported in the results section?

INTERPRETATION OF DATA AND IMPLICATIONS OF THE STUDY FINDINGS

As suggested above, the results of the study are of questionable validity in view of the design deficiencies noted earlier. If, however, one were to assume that the findings are as reported and that a difference in T4:T8 cell ratios exists between the exposed and non-exposed groups, the question remains: what are the implications of such a finding? And, based on study deficiencies, could the results be associated, not with aldicarb, but with another environmental contaminant, etc.? The following comments are submitted based on the assumption that the findings are not due to chance alone.

14. As "pure" water is not known to exist in nature, why wasn't the well water (and municipal water, for that matter) assayed for the presence of other contaminants? In Wisconsin, numerous substances, several of which have been reported to impact the human immune system, are known to occur in the water of shallow private wells. Portage County, Wisconsin contains numerous shallow drinking water wells which are susceptible to the intrusion of many substances, including bacteria, nitrates, organic and inorganic metals, pesticides, viruses, volatile organic compounds, etc.

Immunomodulatory compounds are also known to occur in groundwater used for drinking water in the Central Sands of Wisconsin. In a recent analysis (July 1986) of well water from Marathon County, the following substances were detected: perchloroethylene (30 ppb), chloroform (13 ppb), trichloroethylene (<1 ppb); iron (4.6 ppm) and manganese (75-160 ppb). Manganese has been found to induce immunomodulatory response reported as an increase in the activity of Natural Killer (NK) cells. It is uncertain whether the increased NK cell activity is due to an increase in the absolute numbers of these cells or if the cells simply become more active. If the increase in

INTERPRETATION OF DATA AND IMPLICATIONS OF THE STUDY FINDINGS, con't

T8 cells reported in this study actually reflects an increase in the NK cell component and, as manganese has been identified as a constituent of Portage County groundwater, the authors should discuss this relationship as a possible explanation for the reported increase in numbers of T8 suppressor cells.

15. Additionally, nearly 90% of Wisconsin wells which contained aldicarb at concentrations above the 10 ppb guideline level also contained nitrates at levels exceeding the state and federal guideline of 10,000 ppb. Bacterial contamination in excess of guideline was also found in 13% of 1200 Wisconsin wells surveyed according to a 1985 report published by the Wisconsin Department of Natural Resources. While the impact of nitrates on the human immune function is currently unknown, bacteria have been shown to induce significant immune responses.
16. Aldicarb residue levels in drinking water are known to fluctuate over time. Were the aldicarb residues monitored prior to and during the testing period? When was the study initiated?
17. In a recent EPA review of a comprehensive mouse immunotoxicology study, it was concluded that aldicarb is not immunotoxic at concentrations ranging from 0.1 ppb to 1000 ppb. The T4 helper/inducer and T8 cytotoxic/suppressor T-lymphocytes in man that were evaluated in the human epidemiologic study have phenotypic and functional equivalents in the murine system. That there were no changes noted in the rodent study in plaque-forming cell responses to challenge with sheep red blood cells (a T-cell dependent antigen requiring T-cell help) suggests that the balance of T-helper/suppressor cells was unaffected by exposure to aldicarb. Normal lymphocyte blastogenic responses to mitogens, and to allergenic leukocytes (MLR) in these animals further suggests that aldicarb is not immunotoxic. If indeed the numbers of T8 suppressor cells were increased, wouldn't the authors expect to see a suppressed function in one of the immunologic assays they reported as normal (response to tetanus toxoid, response to mitogens, and the response to the Candida antigen)?
18. Human T8 lymphocytes do not represent a homogeneous cell population, but rather are a "family" of T8 cell subsets. Included in the T8 subsets are suppressor cells and Natural Killer cells. Did the authors attempt to characterize the T8 subset?
19. The study reports a slight increase in the number of TB cells for five individuals reported to have been exposed to aldicarb. The authors suggest that an increase in these suppressor cells would limit or reduce the immune system's capacity to respond to the presence of a foreign protein or infection. This hypothesis conflicts with data presented which show the Candida functional

INTERPRETATION OF DATA AND IMPLICATIONS OF THE STUDY FINDINGS, con't

assay resulted in an elevated response. In the overall assessment, on what basis would the authors exclude the increased Candida response and not similarly exclude the increased T8 values based on normal laboratory ranges for these cells?

20. The study reports an increase in the number of T8 cells, T8 percentage of total lymphocytes, and reduced T4:T8 ratios. Do the numbers of T8 cells and the T8 percentage of total lymphocytes fall into the range of normal variability routinely observed by Dr. Hong? Was the observed increase in T8 cells in the five individuals compared with the "normal" number of T8 cells as observed in a larger population? The data provided in the manuscript are expressed in a summary fashion and do not allow the data to be fully analyzed. It would be very helpful to see a scattergram of individual data points for absolute levels of T8 cells in both the exposed and unexposed groups, to observe more directly the range and distribution of the data. The scattergram in the manuscript of T4:T8 ratios is not sufficient, since the data points represent derived numbers which clearly are influenced to some extent by the percentages of T4 cells in the blood. In addition, it would be very helpful to see a comparable array of data from the larger data set of normals tested in the clinical laboratory performing these assays. Associated with that, and based on the experience with a much larger sample size, it would be helpful to know the established criteria for "abnormal" T8 levels in that laboratory and whether any of the values obtained in the study were in fact in such an abnormal range. It would seem, particularly with the small sample size, that the most appropriate statistical analysis of the T8 data of the exposed versus unexposed groups would be a nonparametric statistical analysis. It would also be interesting to see the results of such a nonparametric analysis of the differences between the exposed group versus the overall normal data from that laboratory. It would also be helpful to see the actual data for T8 cells on the individuals shown in Table 3. How much variation from one sample to another within the same individual was there in the level of T8 cells? The data as represented in the table only provide the mean T8 data and then the T4:T8 ratio, with the latter clearly influenced by data other than the absolute T8 levels.

21. Relative to the measurement of T8 cells, what were the criteria for positivity in the T8 assay? What intensity of fluorescence relative to background controls, was needed to designate cells as positive? This information is important in regard to whether cells with dull fluorescence as well as bright or strong antigenic expression are included within the positive population. Some non-T cells, especially large granular lymphocytes, can be included within the T8 population, since they may express low levels of T8 antigen on their surface. Although the population of large granular lymphocytes is usually low (about 5-10% of peripheral blood mononuclear cells) and only about 30% of large granular lymphocytes express T8, it is possible that an expansion in this population might contribute to

INTERPRETATION OF DATA AND IMPLICATIONS OF THE STUDY FINDINGS, con't

the differences observed. This possibility could have been further evaluated, utilizing two-color fluorescence, to assess the simultaneous expression on individual cells of T3 as well as T8, and also of Leu-11 as well as T8. Without such information, a complete interpretation of these findings is difficult.

22. Most important is the question of the possible functional significance of the observations reported in the manuscript. Since the concerns raised by the data relate mainly to the association between T8 cells and T suppressor activity, it seems very important to obtain data on levels of T suppressor activity in the exposed versus unexposed groups. This might have been determined by examining possible inhibition of 8 cell responses, T cell lymphoproliferative responses, and of production of lymphokines (e.g. IL-2 and/or interferon) by cells taken directly from the women or after generation of suppressor T cells by stimulation with ConA. Also, in regard to the issues raised earlier about the possible contribution of large granular lymphocytes to the data and also in regard to the possibility that suppressor cells might affect Natural Killer (NK) activity, it would have been of considerable interest to directly evaluate NK activity in both groups. This information would have been of particular interest if the number of T8/Leu-11 cells was increased or if there was an overall increase in the number of Leu-11 cells. The data on increased Candida responses in the exposed group are intriguing. This response might have been further assessed by examining reactivity to other microbial antigens, either bacterial (e.g. Streptococcal, Staphylococcal, endotoxin) or virus antigens (e.g. HSV) which might also differ between the groups. Further, to more extensively evaluate the functional import of the in vitro data, skin tests for delayed hypersensitivity, both to Candida and also to other antigens might have been performed. It is unclear whether the observed increased response to Candida reflects increased antigenic stimulation due to environmental exposure, possibly via microbial contamination in the groundwater, or heightened immunologic responsiveness in the exposed group of women.

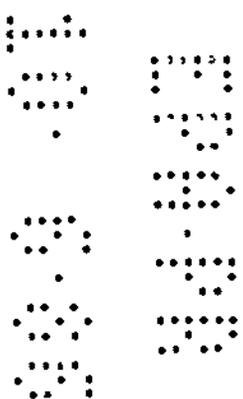
23. In calculations made concerning the estimated daily aldicarb ingestion, the authors used the 14-day fluid-intake logs and the aldicarb residue present in each of the contaminated wells. It is not clear whether these logs were kept at the same time of the year which would have a bearing on water consumption. Based on the author's computations, aldicarb ingestion ranged from 0.3 ug/day to 48.2 ug/day (mean of 15.0 ug/day). These ingestion levels were then used to show (Table 6) a negative correlation between aldicarb intake and the T4:T8 ratio (that is, the higher the aldicarb intake, the lower the T4:T8 ratio). It is of interest to note, however, that the average aldicarb intake for the five individuals showing low T4:T8 ratios was 15.6 ug/day compared with 15.0 ug/day for the exposed group as a whole.

INTERPRETATION OF DATA AND IMPLICATIONS OF THE STUDY FINDINGS, con't

In the generation of dose-response curves it is logical to calculate intake on a body weight or surface area basis. If a 50-kg adult and a 100-kg adult consume equal amounts of aldicarb, one would expect the effects to be much more pronounced in the 50-kg adult. While water consumption is not necessarily correlated with body size, the authors chose to omit this dosage relationship. Due to the missing information (dose/kg body weight), it is impossible to correlate dose with any observed response. As a result, conclusions cannot be made relative to any dose-dependent parameters.

24. The study notes one individual in the control group with a T4:T8 ratio less than 1.3. Was this individual obtaining drinking water from a private well or the municipal water source?
25. While the authors related their findings to animal studies of pesticides and human studies of other environmental contaminants (PCB's, PBB's), why would these authors not compare these data with more relevant epidemiologic studies of pesticide-exposed individuals such as commercial applicators, farm workers, or farmers.
26. Some of these concerns/questions may be resolved by a review of the raw data. Would the Wisconsin Department of Health and Social Services allow independent access to and review of this information?

In conclusion, the study has a number of significant deficiencies and provides no evidence that aldicarb is immunomodulatory.



NOTE TO: Bruce Kapner

SUBJECT: Wisconsin Aldicarb Study

I had already seen an earlier version of Union Carbide's comments on the Wisconsin aldicarb study, prior to the review which I have already submitted. Furthermore, Tina Levine has reviewed all of the reviewers comments including my own. I have nothing to add based on the questions that Union Carbide submitted to Dr. Fiore and the Wisconsin investigators.

Dr. Fiore indicated that he was preparing a response to the Union Carbide questions and would forward a copy of his response to us. If you feel it would be helpful I could comment on Dr. Fiore's response.

Jerome Blondell

Jerome Blondell
Health Statistician
Exposure Assessment Branch (TS-769C)