UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

November 1, 2006

MEMORANDUM

SUBJECT: **Aldicarb** (List A Case 0140, Chemical ID No. 098301). HED Response to Comments Received During the Public Comment Period. DP Barcode No. D331538.

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The responses presented are in reference to comments received following a 60-day public comment period for aldicarb. The comments discussed herein are from the registrant, Bayer CropScience (BSC) and the Natural Resources Defense Council (NRDC) and pertain to the Environmental Protection Agency's Revised Preliminary Human Health Assessment and Disciplinary Chapters for the Reregistration Eligibility Decision (RED) Document for aldicarb dated May 12, 2006. The HED Human Health Assessment and Dietary Exposure Assessment have been revised to reflect comments and errors noted by the registrant. No changes have been made to the Product and Residue Chemistry Chapter, the Toxicology Chapter or Occupational Chapter. All comments pertaining to drinking water exposures will be addressed by the Environmental Fate and Effects Division (EFED).

Response to Bayer CropScience Comments

Document #1: Bayer CropScience Response to the HED Revised Preliminary Human Health Risk Assessment for the Reregistration Eligibility Decision Document (RED) and Re-Evaluation of Dermal Absorption, Sensitivity, and Reversibility Issues: Report of the Hazard Identification Assessment Review Committee

BCS lists 6 main issues; two of which are related to toxicology and are discussed below.

A. Toxicological Endpoint and Reference Dose: BCS believes that the RfD for aldicarb should be derived from RBC cholinesterase data in the human study. This is based on their conclusion that the doses in the human study are closely spaced in the region of interest and thus provide the most appropriate data for calculation of RBC BMD10/ BMDL10 estimates. BCS contends that the doses in the rat studies produced saturated levels of enzyme inhibition, and these are not appropriate for BMD calculation.

HED Response: Consideration of all available toxicity data was used to determine the toxicity endpoints and reference doses appropriate for the aldicarb risk assessment. Criteria utilized in determining the appropriate toxicity endpoints and reference doses included the quality and reliability of the studies and the presence of sound dose-response data. There is a complete toxicology database of oral studies including a human oral study. HED's previous risk assessment (RA) reported risks using multiple endpoints, including those from the human study, to fully characterize risks, but focused on results using the rat RBC cholinesterase inhibition [ChEI] endpoint. This decision reflected the Agency's interpretation of the conclusions drawn by the HSRB prior to issuance of the final report. Based on the final report, which clearly concluded that use of the human study endpoint was appropriate for human health risk assessment, the current risk assessment continues to provide results using all three endpoints considered, but focuses on the results of the human study since these data best reflect human response to the chemical. Because these human data are considered reliable, and the study is considered scientifically valid, at this time the Agency considers the human study to be the most suitable for risk assessment purposes for this single-chemical risk assessment.

With respect to the BCS contention that the rat data are not appropriate for BMD calculation, see detailed responses to comments surrounding BMD analyses below (pages 10-14).

B. Dermal Absorption: BCS believes that the use of a 100% dermal absorption factor in the assessment of occupational risk is an inappropriately conservative assumption. BCS concludes that sufficient data exist to reduce this default value, and a roughly-defined dermal absorption factor default as high as 50% can be adopted with complete confidence.

HED Response: HED agrees that 100% is conservative, as stated in the RA; however, the registrant has not provided any additional data to support/allow the use of a lower dermal absorption factor. The agency has in the past clearly articulated [HED Document No. 013265, 1999] the reasons for the use of 100%. All of the available data were used by the Agency in an attempt to provide a more realistic dermal absorption factor. However, the data do not allow for any credible alternative at this time. Most importantly, BCS has not provided any documentation to support their proposed use of 50%. Therefore, no alteration in the dermal exposure assessment is appropriate at this time.

GENERAL COMMENTS from BCS BCS Line-By-Line Review of the Aldicarb RED Document (only toxicology issues are addressed here). These are identified as to the page of the BCS document where they appear.

(a) On page 9 of 40. EPA's **Page: 7 Paragraph: 3 Lines: 21-22 of EPA RA,** states "… aldicarb induced ChEI has been shown to be reversible in less than 24 hours."

BCS contends that the reversibility time stated in the RA is misleading. BCS states that **Cholinesterase time to recovery is dependent on the dose**. BCS notes that toxicity studies are conducted at doses significantly higher than experienced via the diet to elicit a response; i.e., greater than 10% depression of ChE from baseline. At higher doses, longer recovery times to less than 10% baseline are observed. Their analysis of the data from an aldicarb human volunteer study demonstrated that at 0.019 mg/kg, the recovery time was around one hour (Wyld *et. al.*, 1992). BCS indicated that this was the lowest dose for which a recovery time could be predicted. Since maximum dietary exposure occurs at levels more than 2 orders of magnitude below this level, BCS concludes that at dietary exposure levels, ChE will return to baseline levels extremely rapidly.

HED Response: Aldicarb toxicity is characterized by maximal inhibition of cholinesterase which occurs rapidly followed by recovery typically occurring within hours. A key consideration in risk assessment is appropriate matching of the duration of exposure with the duration of the toxic effect. Typically, HED's food and water exposure assessments sum exposures over a 24 hour period. This 24 hour total is typically used in acute dietary risk assessment. In the case of the aldicarb, because of the rapid nature of aldicarb toxicity and recovery, it may be appropriate to consider durations of exposure less than 24 hours. Conceptually, a physiologically-based pharmacokinetic model and/or biologically-based dose-response model would be available to account for the dynamic nature of exposure, absorption, toxicity, recovery, and elimination of aldicarb in animals and humans. However, such a model does not exist at this time. In the interim, HED has developed an analysis using information about external exposure, timing of exposure within a day, and half-life of ChE inhibition from rats and humans to estimate risk to aldicarb at durations less than 24 hours. Specifically, HED has evaluated individual eating and drinking occasions and used the ChE half-life information to estimate the residual effects from aldicarb from previous exposures within the day.

Table 6 below provides information on the recovery of ChE inhibition in rats and human subjects. For both species, the recovery half-life for RBC ChE inhibition is

approximately two hours. At high doses in rat, the half-life is up to approximately 6 hours in females. The estimates of half-life at the lower doses are most relevant for risk assessment and are thus the focus here. As can be seen in the table, the recovery half life of aldicarb-inhibited AChE in the human is estimated to be on the order of 2 hours using RBC AChE activity This 2 hour recovery half-life is what is used in this refined dietary exposure assessment which incorporates information on eating/drinking occasions. There is some uncertainty associated with the use of the two hour recovery half-life. As discussed in detail below, infants and children are the focus of the current analysis. Although there are dose-response ChE data in juvenile animals exposed to aldicarb, there are no such data to characterize ChE recovery in the young. As such, the Agency has assumed that the half-life to recovery in the young is similar to that seen in adults. The Agency is requiring such data in young animals to confirm this assumption.

Table 6. Recovery half-life information for ChE inhibition following oral exposure to aldicarb in rats and human subjects

Chemical	Brain		RBC	
	Recovery Half-Life Estimate (hrs)	**Upper & Lower Confident Intervals (hrs)**	**Recovery Half-Life Estimate in hrs (dose; mg/kg)**	**Upper & Lower Confident Intervals (hrs)**
Rat	1.52	1.16-1.99	F (< 0.1) 1.10 (0.1,0.3) 2.91 (0.3,0.5) 3.39 (>0.5) 5.90 M (<0.1) 1.91 (0.1,0.3) 1.20 (0.3,0.5) 1.62 (>0.5) 1.50	F 0.50-2.40 1.96-4.33 2.35-4.90 3.52-9.91 M 1.31-2.79 0.87-1.64 1.19-2.21 0.80-2.82
Human	N/A		2.07	1.74-2.46

(b) On page 9-10 of 40. EPA's **Page: 7 Paragraph: 4 Lines 30-36** on increased sensitivity in PND 17 pups. BCS states that the only increased sensitivity seen in the PND 17 animals was in the dose needed to achieve "the MTD (more accurately should be called the lethal dose)" and brain ChE depression. Administration of a bolus dose directly to pups at dose levels that produce a high degree of ChE inhibition can misrepresent the effects associated with lower levels that might occur with relevant dietary exposures.

According to BCS, this difference in outcome arises because the increased sensitivity of neonatal animals to AChE inhibition results not from pharmacodynamic differences in target enzyme (AChE) sensitivity (relative AChE inhibition for a given tissue concentration of the proximal inhibitor), but from age-dependent pharmacokinetic differences in the capacity of the metabolizing enzymes that determine the tissue concentration of the proximal inhibitor. The generally lower capacity of metabolic enzymes in neonatal animals may result in a greater internal exposure for the same administered dose. Importantly, due to the nature of capacity-limited metabolism, as described by the Michaelis-Menton equation, the impact of these age-dependent metabolic differences can be much greater at doses that exceed the relatively limited

metabolic capacity of the neonate than at doses that are well below saturation of metabolism. BCS concludes that an FQPA safety factor is not required for aldicarb.

HED Response: Although these are reasonable assumptions, sufficient kinetics data to demonstrate the lack of a difference at the "much lower levels of exposure that are relevant for an FQPA risk assessment" Additionally, a 2X difference in response was observed in both sexes at each dose level tested [see table below], including the 0.05 mg/kg dose level where a "high degree of inhibition" was not demonstrated. At the lowest dose tested [0.05 mg/kg], the largest difference between the age groups was observed; i.e., the difference in males was 2.3 and difference in females was 2.4. Additionally, the ratio of the BMDs for adults and pups indicates a 2X difference [brain BMD10s ranged from 0.014 to 0.020 in juvenile animals and 0.024 to 0.031 in adult animals].

Moser Replication Study - Brain Cholinesterase Data		
Age/Sex/Dose [mg/kg]	Males	Females
ADULT		
0	4.96±0.16	4.80±0.10
0.05	4.37±0.12 [12]	4.30±0.12 [10]
0.1	3.64±0.17 [27]	3.78±0.18 [23]
0.2	2.78±0.31 [44]	2.49±0.27 [48]
0.3	2.41±0.56 [51]	2.19±0.19 [54]
PND 17		
0	3.95±0.34	3.80±0.19
0.05	2.83±0.11 [28] (2.3)^	2.89±0.23 [24] (2.4)
0.1	2.38±0.27 [40] (1.5)	2.02±0.11 [47] (2.0)
0.2	1.04±0.17 [74] (1.7)	1.17±0.18 [69] (1.4)
0.3	0.64±0.07 [84] (1.6)	0.90±0.11 [76] (1.4)

.. [% inhibition]; ^ (ratio of pup:adult % inhibition)

It is to be noted that the peak effect time used in the Moser study was determined for both age groups based on clinical signs. It is to be noted that clinical signs were observed more frequently in adult animals versus the young animal in other studies on aldicarb. Although the same peak-effect time was determined for both groups, it is possible that the adult animal reached a similar % ChEI as the pup but at a different time post dose than was measured in this study. Data that are not available to address the issue of sensitivity include an assessment of whether the adult animals reach a similar % ChE inhibition as the pups at a different time point (earlier or later) post exposure. In order to address this aspect and others, a comparative cholinesterase assay would be necessary for aldicarb.

Although none of the guideline studies on aldicarb showed evidence of sensitivity, it is to be noted that ChEI is not monitored in the rat and rabbit developmental toxicity studies, and measurement of ChEI in the reproduction study occurred in blood samples collected

only at study termination; ChE data between young and adult animal were not compared; time sample collected post exposure for ChE activity assessment is not known.

BCS believes that the developmental neurotoxicity study [DNT] is the most appropriate study for assessing sensitivity, and sensitivity was not demonstrated in the DNT on aldicarb. HED agrees that the DNT is an appropriate study for assessing sensitivity. However, in the case of aldicarb, the assessment of ChE activity was performed on samples collected **2 hours** after dosing of the dams. Effects on ChE following aldicarb exposure are expected to peak sooner. Data from other studies on aldicarb indicate that peak ChE inhibition occurs as early as 30-45 minutes post dose. Based on BCS own arguments on reversibility, this 2-hour time point for the assessment of ChEI is not appropriate in this case. Because of the timing of sample collection in this DNT, it is unclear whether accurate ChEI values were obtained or that peak inhibition was measured. It also complicates interpretation of the maternal ChEI values and the apparent lack of ChEI at the low- and mid-dose levels. Additionally, since there was no indication of whether the pups nursed prior to their ChE assessment, and there is no information regarding the timeframe for aldicarb to reach the milk. The apparent lack of ChEI in the pups cannot be considered definitive evidence that the young animal is not more sensitive. For aldicarb, the DNT does not provide a definitive assessment of sensitivity. The FQPA safety factor of 2X is supported by reliable data and is retained.

With respect to the statement that the route of administration in the DNT was the most appropriate for assessing sensitivity in infants and children, it is to be noted that dosing was to the adult (dam) *via* gavage. The young animal was not dosed directly. Although some infants are nursed, children and other infants are directly exposed to food.

(c) On page 11 of 40. EPA's **Page: 7 Paragraph: 5 Lines 38-42** regarding EPA's conclusion that there is a two-fold difference between animals and humans with respect to toxic responses. BCS points out the similar level of inhibition in both species at the common dose level of 0.05 mg/kg. Since the 2-fold difference is based on the BMDL10s calculated for the two species [0.02 mg/kg and 0.013 mg/kg], it is BCS contention that since enzyme inhibition was saturated at the majority of the rat doses used in the BMDL10 analysis, the rat data are not reliable for comparison with the human BMDL10 analysis.

<u>HED Response</u>: Based on the current use of the human data in the risk assessment, this is a moot point for the single chemical assessment. However, the Agency does not agree that the rat BMDL10 analysis is not reliable [see detailed responses to comments surrounding BMD analyses below (pages 10-14)].

(d) BCS states that a graphical illustration of the dose-response data in human versus rat suggests an apparent continuation of the response across both species from 0.01 to 0.1 mg/kg and further demonstrates the similarity in the magnitude of the response in both species at the common dose level of 0.05 mg/kg.

HED Response: It is to be noted that the lowest dose tested in the rat studies is 0.05 mg/kg. There are no data at the 0.01 mg/kg dose level for the rat.

(e) On page 13 of 40. BCS comments on EPA's **page 8, paragraph 2, lines 14-21**, BCS states that "the implication in EPA's revised preliminary risk assessment document that the Human Studies Review Board (HSRB) considered the human data appropriate only to inform the interspecies factor is misleading." BCS states that the HSRB report contains no specific comment by the Review Board regarding the use of the human data only to inform the interspecies factor.

HED Response: HED's charge to the HSRB: Please comment on the scientific evidence that supports whether the aldicarb human study is sufficiently robust for reducing the inter-species uncertainty factor. The HSRB's response to this charge was:

> (1) The HSRB concluded that the aldicarb human study appears to be a scientifically valid study, suitable for use in both the aggregate risk assessment and the cumulative risk assessment.
>
> (2) The Board stated that the dose-response data from the human study appeared such that BMD and BMDL can be calculated.
>
> (3) The Board concluded that the results of the human study could be used in the WOE analysis to determine a NOEL for RBC cholinesterase and clinical signs in males and that the RBC cholinesterase demonstrated a dose-dependent and time-dependent pattern of inhibition in both males and females.

While HSRB did not address directly the charge; i.e., whether the study could inform the interspecies factor, the HSRB's draft report indicated that (1) the human study is sufficiently robust (appears to be scientifically valid) and suitable for use in risk assessment; (2) it can be used to calculate BMD/BMDL, which HED used to compare to the rat BMD/BMDL; and (3) it can be used in the **weight of analysis** [WOE]. The Agency's interpretation of the draft HSRB final report was that the human study could be used to inform the inter-species factor.

(f) On page 15 of 40, BCS states that none of the rat data have been subjected to the rigorous reviews and extensive deliberations to which the human data have been subjected.

HED Response: This is not an accurate statement. HED has extensive experience in the review of animal toxicology data. All of the rat data on aldicarb have been through numerous assessments over the years by the Agency review committees, including the HED HIARC, RfD, and TES committees, CPRC/CARC, and an Agency non-OPP expert review committee. Additionally, the acute neurotoxicity, subchronic neurotoxicity, and developmental neurotoxicity studies are all guideline studies, which were all performed using adequate numbers of animals per dose group for statistical assessment. The non-guideline studies by Moser used the more appropriate method for cholinesterase

measurement for a carbamate chemical, and an Agency non-OPP expert review committee reviewed these studies. Therefore, the Agency believes that both the human and animal data have gone through similar thorough analysis.

Document #2: Bayer CropScience's Assessment and Rebuttal of the Reference Dose as Proposed by EPA in the Health Effects Division Revised Preliminary Human Health Risk Assessment of Aldicarb Issued on May 12, 2006

It is to be noted that several of the issues/concerns in this document are the same as in Document #1 above and are not repeated here.

(a) On page 6 Weight of the Evidence Establishment of the RfD: Regarding the extensive toxicological database on aldicarb and the fact that most of the data are in the rat, the registrant notes that the doses tested in these studies typically produced ChE inhibition of 30% and greater with often maximal or near maximal inhibition at several doses. In contrast, the human study is noted to cover a dose-response range that includes doses around the benchmark response of 10%, as well as dose levels causing clear inhibition of ChE. **Studies with one or more doses near the level of the BMR are generally considered to provide a better estimate of the BMD while studies with responses at or near the maximal response level should not be considered for BMD analysis due to saturation.**

HED Response: With regard to the issue of appropriate BMD analysis, [see detailed responses to comments surrounding BMD analyses below (pages 10-14)].

(b) On page 8 of 16. The authors state that the RBC ChE results indicate that the 10% BMR is below 0.05 mg/kg in both rats and humans, and inhibition of the enzyme begins to plateau above 0.1 mg/kg **in both species** (emphasis added).

HED Response: With regard to the statement that in both rats and humans, inhibition of enzyme **begins to plateau above 0.1 mg/kg** (also on page 16 of 86)**,** it is to be noted that human data at the 0.1 mg/kg dose level are not available from the human study reviewed by the HSRB. Also, the statement here regarding a plateau **in both species** is in contrast to the rebuttal statement on page 14 of 40, which indicates that the "dose-response does not appear to produce saturation of cholinesterase in humans compared to the rat". These two statements are conflicting.

(c) On page 9 of 16, the authors state that, given the similarity of ChEI response between rat and human at the common dose of 0.05 mg/kg, one would expect that a BMD analysis of data in the same dose-response range for each species should produce similar BMD10 and BMDL10 values for both rat and human. EPA's calculation of **higher BMD estimates for rats versus human is most likely an artifact due to the inclusion in the analysis for the rat of multiple dose levels producing saturation of ChE inhibition at the high doses.** Combining the rat studies reinforces the bias of each study's weakness,

i.e. multiple dose levels producing a saturated dose-response, and distorts the BMD estimates.

HED Response: [see detailed responses to comments surrounding BMD analyses below (pages 10-14)].

(d) Also on page 9, the authors state that since the BMD estimates determined for the rat cannot be considered reliable due to the distorted influence of a saturated dose-response, any quantitative conclusions regarding interspecies differences derived from them are equally unreliable.

HED Response: This is a moot point. However, see detailed responses to comments surrounding BMD analyses below (pages 10-14).

(e) On page 10 of 16 (in discussing Figure 1), it is stated that the dose-response does not appear to produce saturation of cholinesterase inhibition in humans compared to the rat.

HED Response: This statement is not supported, based on the lack of human data at dose levels where an apparent saturation was observed in the rat. As can be seen from the figure, at 0.05 mg/kg the response is comparable (human and rat) and at the next higher dose for each species (human 0.06-0.075 mg/kg *vs* rat 0.1 mg/kg), the response is also quite similar. Lacking a higher dose in the human, one cannot speculate that at 0.2, 0.4, 0.5, and 0.6 mg/kg dose levels the human would not have a similar response as the rat. Having shown a similar response at two similar dose levels, there does not appear to be a basis for concluding there would be a difference in response between the two species at dose levels both above and below these two dose levels.

(f) In the Sensitivity to Infants and Children section (page 12), it states that the only increased sensitivity seen in the PND 17 animals was in the dose needed to achieve "the MTD (more accurately should be called the lethal dose)" and brain ChE depression. Administration of a bolus dose directly to pups at dose levels that produce a high degree of ChE inhibition can misrepresent the effects associated with lower levels that might occur with relevant dietary exposures. Additionally, the authors conclude that the overall weight-of-evidence supports that an extra FQPA safety factor is not required for aldicarb.

HED Response: This comment is the same as in Document #1 and is addressed above.

Detailed Responses to Comments Surrounding BMD Analyses

- **Responses to comments surrounding BMD analyses including issues such as "saturation" of the ChE inhibition and Bayer CropScience's preference for the analyses provided by OPCum Risk over the more complicated analysis combining datasets**

There are two main themes in the comments from Bayer CropScience surrounding the BMD analysis of the rat data: saturation of ChE inhibition distorts BMD estimates at the low end of the dose response curve and evaluating one data at a time is preferred over combining data from multiple studies.

Bayer CropScience makes the statement that "studies with responses at or near the maximal response level should not be considered adequate for BMD analysis due to saturation." The Agency's BMDS web tutorial is listed as the reference for this statement. HED looked at this reference and contacted ORD scientists involved in developing BMDS. The following quotes were extracted verbatim from the web tutorial and seem to be the source of the Bayer CropScience statement.

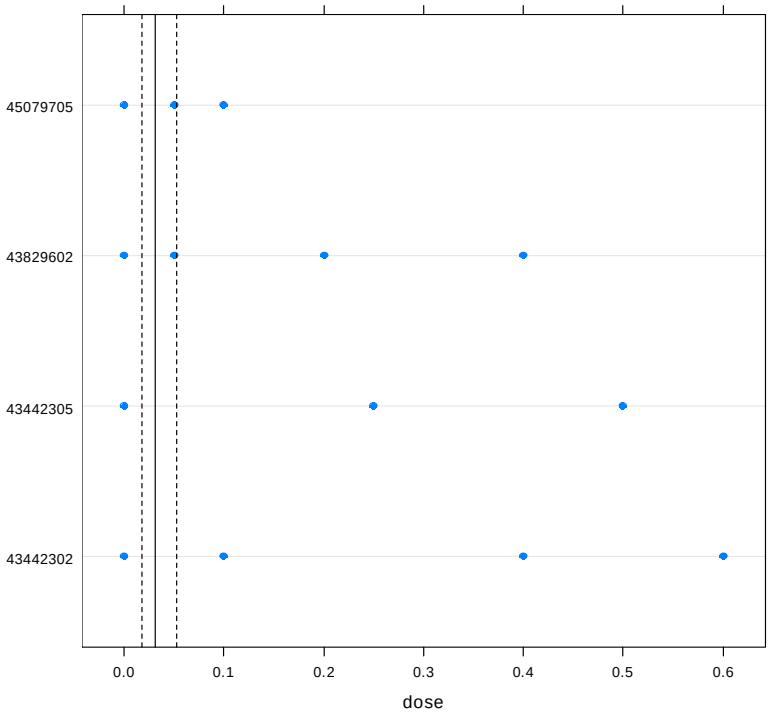
> **"Assess the Fit of the Models.** Retain models that are not rejected using a p-value of 0.1. Examine the residuals and plot the data and models; check that the models adequately describe the data, especially in the region of the BMR. (Sometimes it may be necessary to transform the data in some way or to drop the highest exposure group(s) (e.g., if the behavior at high exposures can be attributed to early mortality or enzyme saturation effects) and repeat the modeling in order to get a good fit.)
>
> **Are the data appropriate for a BMD analysis?**
>
> Once the critical endpoints have been selected, data sets are examined for the appropriateness of a BMD analysis. The following constraints on data sets to use for BMD calculations should be applied:
>
> There must be at least a statistically or biologically significant dose-related trend in the selected endpoint; and
>
> The data set should contain information relevant to dose-response for modeling. determination of the amount of information about the dose-response that is available need not be quantitative or technical. For example: A data set in which all non-control doses have essentially the same response level provides limited information about the dose-response, since the complete range of response from background to maximum must occur somewhere below the lowest dose: the BMD may be just below the first dose, or orders of magnitude lower. When this situation arises in quantal data, especially if the maximum response is less than 100%, it is tempting to use a model like the Weibull with no restrictions on the power parameter, because such models reach a plateau of less than 100%. This

> situation can result in seriously distorted BMDs, because the model predictions jump rapidly from background levels to the maximum level. In principle, other models could be found that force the BMD to be anywhere between that extreme and the lowest administered dose. Thus the BMD computed here depends solely on the model selected, and goodness of fit provides no help in selecting among the possibilities. (See the quantal data examples in the Technical Guidance (EPA, 2000) Appendix for an example of this situation): "

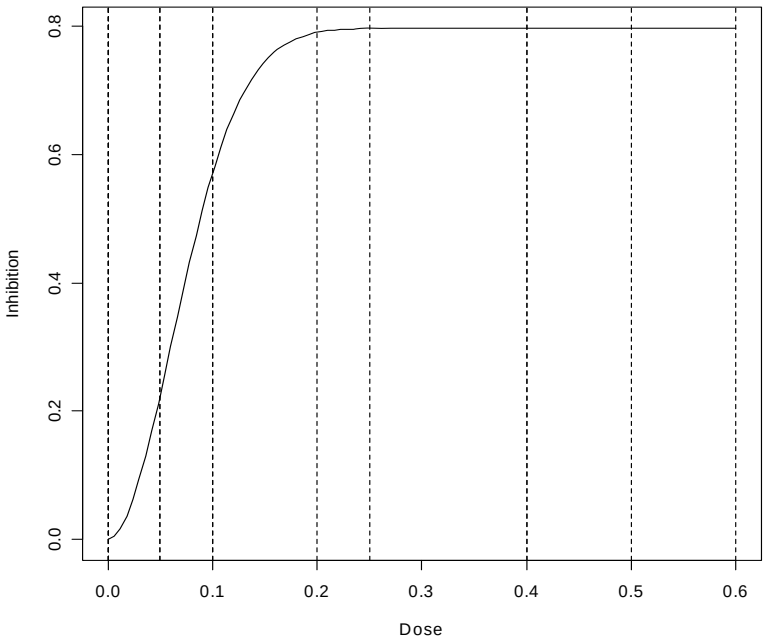
For some of the quantal models in the BMDS (like the example provided in the BMDS tutorial text), extreme high dose data can sometimes cause a distortion of the BMD at the lower end of the dose response curve. Because of this, it may be appropriate to drop a high dose in a BMD analysis for some datasets. Dropping the high dose is allowed for in the OPCum Risk program. However, as Bayer CropScience also accurately states, the Agency's exponential dose response model is sufficiently flexible to allow for a plateauing of ChE inhibition at a response level lower than 100% thus significantly reducing this potential distortion.

Moreover, in the aldicarb analysis, the Agency has used data from multiple studies simultaneously which provides a more robust analysis of the entire dose response curve compared to evaluating one dataset at a time. By modeling the combined datasets, the Agency has taken advantage of the increased number of dose levels to get a better idea of the shape of the dose-response curve. This translates into the ability to fit more complicated models which more accurately reflect the true dose-response shape. As Bayer CropScience shows in Figure 1 (pg, 10), there seems to be a 'shoulder' at the very low end of the dose response curve where the slope is fairly shallow for rat data. The OPCum Risk program can not account for this shallow slope at the low end of the dose response curve. In 2001 when the Agency was in the early stages of developing its OP cumulative risk assessment, the Agency developed the OP Cum Risk program. This program has been reviewed by the SAP and continues to be very helpful in risk assessments of ChE inhibiting chemicals. However, this program has some limitations. Specifically, based on comments from the SAP and the stakeholders, the Agency's revised dose-response assessment refined its analysis to include the possibility of a low dose shoulder region. The Agency has shown that approximately ½ of the OPs exhibit this low dose shoulder and approximately ½ do not. Furthermore, the Agency learned that combining data from multiple studies improved the ability to model the complete shape of the dose response curve, including the low dose shoulder region. The Agency's experience with the OPs informed the analysis for the *N*-methyl carbamates. Specifically, the sophisticated analysis included in the *N*-methyl carbamate cumulative assessment includes the possibility for this low dose shoulder.

Based on the rat ChE data, 'saturation' or plateauing of ChE inhibition seems to occur at or near 80% inhibition. Here is a plot of doses available in the four studies used in the rat BMD analysis. Note that two of the studies have only three dose levels (including control), but, together, there are 8 dose levels ranging from near the BMD_{10} to much higher levels of inhibition. The estimated BMD and 95% confidence limits are indicated with vertical lines:



Here is a plot of the predicted RBC AChE inhibition, with the dose-levels in the different studies indicated by vertical dashed lines.



Because of the data from 8 different dose levels parameters for both the low-dose shoulder and the high dose plateau (that is, lg and tz) could be estimated.

Mathematically, in the analysis of the aldicarb RBC data, the power parameter (actually, the log of it, lg) of the dose response curve was estimated to be greater than 1, and is fairly significant (nominally, P ~ 0.00033 for the test against the null hypothesis that the power is 1). OPCumRisk is unable to estimate the power parameter, effectively fixing that parameter to 1.0—and thus overpredicting ChE inhibition at the low dose end to some degree.

The Agency was able to estimate both the low-dose shoulder and the high dose plateau (that is, lg and tz) because data from several studies that span a range of doses were used. Thus, by combining the information from multiple studies, the Agency was able to fit the entire dose response curve. If the Agency were to follow Bayer's recommendation not to combine studies, and tried to fit models to individual datasets, information from several dose levels would be ignored---because they would be useless for estimating dose-response parameters. A couple of the studies would contribute at most one useful dose level for the dose-response analysis if the analysis were conducted one at a time, whereas, when analyzed together, a more complete description of the dose-response curve is achieved. The FIFRA SAP has supported the Agency's combining of data from multiple studies in dose-response efforts with the ChE inhibiting chemicals. For example, in the 2001 report, the panel states:

> *"There are several advantages of combining estimates from multiple datasets compared to using estimates derived from single datasets/points. Combining data increases the precision of estimates, incorporates the variability among data sets into the overall estimate of uncertainty (standard errors or confidence limits), and maximizes the use of the available information."*

Another component of the Agency's analysis is the ability to use all the time course data in estimates of half-life to recovery---time course analysis is not a component of the OPCumRisk program. Lastly, the Agency's analysis accounts for repeated measures (ie, RBC ChE inhibition from the same animal more than one time) and thus includes within animal variability. Because one dataset is analysed at a time in OPCum Risk, repeated measures is not accounted for when using OPCum Risk.

The Agency acknowledges that the statistical procedures used in the aldicarb analysis (and for other members of the *N*-methyl carbamate common mechanism group) is highly sophisticated. The Agency has presented its approach to the FIFRA SAP at two meetings (February and August, 2005) and received positive feedback from the panel. The approaches are described in detail in Chapter B of the Preliminary Cumulative Risk Assessment of the *N*-methyl carbamates and the associated "B" appendices. The "B" appendices contain numerous files, including the R code used in the statistical analysis, the actual ChE data used, and the output in pdf format. On August 18, 2006, the Agency confirmed the public availability and ease of access to these files by extracting them from http://www.epa.gov/scipoly/sap/meetings/2005/index.htm#feb22 ("All Meeting Documents"). The Agency successfully downloaded the datasets in excel format (II.B.1-1 & -2) and the pdf versions of the "B" chapter and associated appendices, including the outputs of the aldicarb rat BMD estimates (II_B_2_a & _b).

- **Endpoint Selection**

Bayer's comments seem to infer than they believe that data from plasma or whole blood ChE were used in the Agency's BMD analysis. This is incorrect. The Agency did not include data from plasma or whole blood in the BMD analysis. As indicated on pg 4 of the EPA's June 30, 2005 analysis:

> "We need to select out the records for ***red blood cells*** of animals dosed via gavage. Drop records with missing values for cheact, and any The one aggregated study, 43442305, used multiple chemicals: aldicarb, aldicarb sulfoxide, and aldicarb sulfone. Drop everything but the active ingredient. However, the control group in that study used NA to code the control chemical, so we need to retain those records. Finally, make sure we have a value for sd for records with n greater than 1.
>
> > dta <- CleanUp(subset(wrkdata[["AggData"]], mrid %in% MRIDSforRBCDR[["Agg"]] &
> > + sctn %in% "***RBC***" & dsmtd == "GAVAGE" & !is.na(cheact) & (n ==
> > + 1 | !is.na(sd)) & (is.na(ta) | ta %in% c("AI")), select = KeepVars))"

Document #3: Responses to: Bayer Crop Science Response to the Revised Anticipated Residues and Dietary Exposure Analyses for the HED Human Health Risk Assessment

Bayer CropScience noted four areas where they considered inappropriate data had been used or data excluded as follows:

1. Application of Potato Processing Factors
2. Conversion of residues to aldicarb sulfone equivalents rather than aldicarb equivalents
3. Sweet potato Residues Data Source
4. Incorporation of Effects of Cholinesterase Reversibility

In response the comments made by Bayer CropScience, the dietary assessment was revised to include updated sweet potato PDP data, missing cooking factors, and to convert from aldicarb sulfone equivalents to parent aldicarb.

The sweet potato PDP data used were from the years 1999, 2003 and 2004. These data were used for all partially blended sweet potato food forms. In previous assessments, potato PDP data were used for all food forms. For all nonblended foodforms, potato data from the 1997 Special Survey were used since HED use of single serving data for non-blended commodities is more protective. See Attachment 3 for RDF 56SWmcsp for residue inputs.

Several cooking factors for boiled and fried potatoes were erroneously not used in the previous assessment as not by the registrant. This was corrected in this revised assessment.

HED also converted risks estimates from aldicarb sulfone equivalents to aldicarb *per se*. HED concurs with the registrant that since current methods analyze parent aldicarb and metabolites sulfoxide and sulfone as individual chemicals and no longer utilize the common moiety method which converted parent and metabolites to sulfone equivalents, it is no longer appropriate to convert all residues to aldicarb sulfone. Consequently, HED multiplied all risk estimates by 0.86 to convert the sulfone equivalents to aldicarb *per se*.

With respect to the issue of incorporation of the effects of cholinesterase reversibility, the Agency acknowledges receipt of the dietary assessment which utilized the CARES-Dietary Minute Module. The Agency is currently reviewing the submitted data and assessment and will make a determination on its applicability to the Aldicarb Human Health Assessment at a later date. See also response under *Document #5* in this memorandum.

Document #4: Bayer CropScience Response to the Update of Incident Data Review of April 10, 1996.

Based on our review of the BCS submission, Bayer's comments raise no substantive issues and do not warrant a response from us at this time. Since the previous review of the PCC/TESS data and IDS data only covered up through 1998 and 1999, respectively, CEB recommends updating the Incident Review PCC/TESS data through 2005 when the 2004 and 2005 data become available in the near future. A review of the IDS data on aldicarb should also occur at this time.

Document #5: Aldicarb Acute Dietary Risk Assessment Including Food and Drinking Water and Document #6 Human Health Risk Assessment for Use on Currently Registered and Pending registrations as of May 2006.

HED acknowledges the receipt of the acute dietary risk assessment and human health risk assessment conducted by the registrant using its Dietary Minute Module. The Agency is currently reviewing the submitted data and assessment and will make a determination on its applicability to the Aldicarb Human Health Assessment at a later date.

HED has; however, further refined the acute aggregate risk from food and groundwater by incorporating the time and amounts consumed for each eating occasion from the USDA CSFII food diaries to estimate exposures and risks on each eating occasion throughout the day. This refined assessment also incorporated the available toxicological data which indicates that the estimated half-life for cholinesterase inhibition resulting from aldicarb exposure is 2-hours or less. Exposures and risks using this approach were calculated using the DEEM model coupled to a SAS® program which accounted for cholinesterase regeneration. To verify these DEEM-based eating occasion results, the Agency's

Office of Research and Development's Stochastic Human Exposure and Dose Simulation (SHEDS) model was also used to conduct an eating occasion analyses for aldicarb. The SHEDS eating occasion results are similar to the DEEM-based results, providing additional assurance regarding the accuracy of these computations. SHEDS was also used to conduct further sensitivity analyses on the half-life parameter, as well as addressing issues regarding both direct and indirect drinking water consumption. Detailed information on the methods used to derive the aggregate exposures are presented in the document titled "Aldicarb: Acute Dietary Exposure Assessment to Support the Reregistration Eligibility Decision" [S. Nako and J. Xue, 11/01/06].

Table 13 presents the respective DEEM-FCID® and SHEDS®' estimated risks at the *per capita* 99.9th percentile using a 2 hour half-life for cholinesterase inhibition. These eating occasion results are based on several major assumptions: (i) 2 hour half-life, (ii) allocation of direct drinking water consumption based on 6 equal and fixed occasions, and (iii) no modifications to the amount of indirect drinking water consumed as reported in the CSFII diaries for infants. Direct water is water that is consumed from the tap and indirect water is considered water that is used in the preparation of food.

It should be noted that incorporating eating occasion analysis and the 2 hr. recovery half life for aldicarb into the *Food Only* analysis does not significantly change the risk estimates when compared to baseline levels (for which a total *daily* consumption basis – and not eating occasion - was used) From this, it is apparent that modifying the analysis such that information on eating occasions and aldicarb half life is incorporated results in only minor reductions in estimated risk: generally on the order of several percent, at most, for all age groups. However, risk estimates for which food and drinking water are jointly considered and incorporated are reduced considerably (by a factor of 2 or more in some cases) compared to baseline and is not unexpected: infants receive much of their exposures from indirect drinking water in the form of water used to prepare infant formula.

National Resources Defense Council (NRDC) Comments

1. NRDC disagrees with the use of human study to inform interspecies uncertainty factor, stating that the Human Studies Review Board (HSRB) "warned that the human study was inadequately powered and thus the possibility of a false negative, that is, the inability to detect an adverse effect where it occurs, is "a real concern"." Also, NRDC contends that the HSRB concluded that the study failed to fully meet the specific ethical standards prevalent at the time the study was conducted. Therefore, NRDC concludes that "EPA's consideration of and reliance on the Aldicarb human study is arbitrary and capricious since the study's ethical violations are significant."

HED Response: Although the HSRB indicated that the human study had several limitations, the final report stated the following: (1) the aldicarb human study appears to be **a scientifically valid study**, **suitable for use** in the risk assessment; (2) the dose-response data from the human study appeared such that BMD and BMDL can be calculated; (3) the results of the human study could be used in the WOE analysis to determine a NOEL for RBC cholinesterase; and (4) the **RBC cholinesterase data from the human study were reliable** and demonstrated a dose-dependent and time-dependent pattern of inhibition in both males and females.

2. NRDC questions why EPA dropped the 10X LOAEL to NOAEL uncertainty factor, which HED presented to the HSRB as the endpoint for risk assessment.

HED Response: As stated in the May, 2006 revised preliminary RA, dose-response modeling is preferred over the use of NOAELs/LOAELs since NOAELs and LOAELs do not necessarily reflect the relationship between dose and response for a given chemical, but instead reflect dose selection. Dose-response modeling is considered a higher tier assessment providing Points of Departure (PODs) that are more accurate than the use of NOAELs/LOAELs and uncertainty factors. In order to evaluate the appropriate point of departure (PoD) for ChEI, the Agency considered the benchmark dose estimates developed from both the rat and human data.

The assessment of the data presented to the HSRB was based on the use of NOAELs/LOAELs and default uncertainty factors; e.g., LOAEL to NOAEL. The May, 2006 and the current assessment are based on dose-response modeling. Therefore, the 10X LOAEL to NOAEL uncertainty factor is not appropriate.

3. NRDC disagrees with the use of the oral data for inhalation exposure assessment

HED Response:

(2) Aldicarb is a Toxicity Category I compound for all routes of exposure
(3) ChEI is the toxicity of concern; the oral assessment is based on ChEI and is being used pending submission of an acute inhalation study to assess ChE activity and recovery.
(4) An inhalation Toxicity Category of I results in label requirements of protective equipment for workers. There are no residential uses
(5) A subchronic inhalation study was a datagap. Although this study is no longer required (an acute inhalation study is now required), it is Agency policy not to apply an additional uncertainty factor for lack of this route-specific study.
(6) There is a potential for inhalation exposure from aldicarb-treated tobacco, but there are no residential uses or agricultural uses that would result in residential exposure to the general population. Although exposures can occur for occupational handlers loading or applying aldicarb granulars, no postapplication exposure is expected because aldicarb is soil-incorporated at planting.

4. NRDC disagrees with the conclusion that chronic exposure assessment is not needed.

(1) There is a complete database on aldicarb, and there is no indication that toxicity increases on long-term exposure. In fact, the NOAEL for effects other than ChEI is greater than that for ChEI following various exposure scenarios. Therefore, performing a chronic risk assessment based on an endpoint other than ChEI would not be protective and would not make sense. Additionally, the NOAEL following repeat exposure is higher than that following acute exposure, which supports the decision that chronic exposure can be considered a series of acute exposures and a separate assessment is not needed.

5. NRDC implies that the HSRB had "a real concern" (NRDC's emphasis) with respect to the statistical analysis and the fact that the study was likely under-powered.

HED Response: HSRB discussed the statistical analysis of the human study, which was considered a weakness of the study. However, they concluded that, although "it is clear that the statistical power of the study was low, the data do show a very clear and predictable dose- and time-dependency in the RBC cholinesterase data." Further, it was concluded that the results of the human study could be used in the WOE analysis to determine a NOEL for RBC cholinesterase.

General Comments: Several respondents reiterate BCS contention that the animal data have not been subjected to the rigorous reviews and extensive deliberations to which the human data have been.

HED Response: As noted previously in response to BCS comment on this issue, the majority of the toxicology data available on aldicarb are from guideline studies in animals. HED has extensive experience and a long history in reviewing animal toxicology data. All of the rat data on aldicarb have been through numerous evaluations over the years by the Agency review committees, including the HED Hazard Identification Review Committee [HIARC], RfD Peer Review Committee, and Toxicology Endpoint Selection [TES] Committees, and an Agency non-OPP expert review committee. Additionally, the acute neurotoxicity, subchronic neurotoxicity, and developmental neurotoxicity studies are all guideline studies, which were all performed using adequate numbers of animals per dose group for statistical assessment. The non-guideline rat studies by Moser used the more appropriate method for cholinesterase measurement for a carbamate chemical, and an Agency non-OPP expert review committee reviewed these studies. Therefore, the contention that the animal data review was of a lesser quality than that of the human study is an inaccurate characterization.