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TOXIC SUBSTANCES

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MEMORANDUM

SUBJECT: Atrazine: Response to Syngenta's Comments on the EPA's April 16, 2002 Revised Human Health Risk Assessment and Associated Documents for the Reregistration Eligibility Decision (RED). PC Code: 080803. DP Barcode D284708.

FROM: Catherine Eiden, Branch Senior Scientist
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Health Effects Division

TO: Kimberly Lowe, Chemical Review Manager
Special Review and Reregistration Division

Please find attached the response document to Syngenta's comments on HED's April 16, 2002: Revised Human Health Risk Assessment for the Reregistration Eligibility Decision (RED).HED responders include: Catherine Eiden, Gary Bangs, and Linda Taylor. EFED responders include Mary Frankenberry and Jim Lin.

Executive Summary

Syngenta provided an executive summary of all of their specific comments on the revised human health risk assessment. They also submitted several documents as attachments containing new data and information relevant to the risk assessment. The results of analyses and review of the additional data, and responses to these comments are contained in this document.

Attachment 1: The Effects of Atrazine on the Sexual Maturation of Female Alderley Park-Wistar and Sprague-Dawley Rats.

In a special study [MRID 45722401] that involved four separate experiments, 8-10 Alpk:ApfSD (Wistar-derived; AP) female rats/dose group and 8-10 Sprague-Dawley (SD) female rats/dose group [20-21 day old] were dosed once daily *via* gavage [10 mL/kg] with atrazine [98.2%], vehicle [carboxymethylcellulose (CMC)], or Antarelix™ [a centrally-acting GnRH antagonist] for up to 25 days. The dose levels of atrazine were 10, 30, and 100 mg/kg. Antarelix was dosed at 0.3 mg/kg. The first two experiments involved the determination of uterine weight on either postnatal day 30 [start of puberty] or on postnatal day 33, when uterine growth was assumed to have been completed.

Alpk:ApfSD (Wistar-derived; AP) female rats: Atrazine: *Uterine growth*: There was a dose-related decrease in uterine weight following exposure to atrazine from postnatal day [PND] 22 to PNDs 29 [8 doses], 32 [11 doses], and 42 [21 doses]. At the high-dose level, the largest decrease in uterine weight was observed in the group receiving the 11 doses [PND 22-32], and the smallest decrease was observed following the longest exposure [PND 22-42]. The magnitude of the decrease in body weight [93% of control]/body-weight gain [87% of control] observed at the high-dose level following the 11-dose regimen does not account for the magnitude of the decrease in uterine weight [blotted 55%/dry 50% lower than control]. At the mid-dose level, the decrease in uterine weight [blotted 22%/dry 16% lower than control (PND 22-29); blotted 18%/dry 19% lower than control (PND 22-42)] was not statistically significant but is considered treatment-related. Body weight and body-weight gains of the mid-dose females were comparable to the control values. *Vaginal opening [VO]*: At the high-dose level, there was a statistically-significant delay in VO [PND 41] compared to the control [PND 38] following the PND 22-42 dosing regimen. Antarelix: *Uterine growth*: In comparison, the rats exposed to ANT showed a lack of uterine growth, and in contrast to the atrazine findings, the magnitude of the decrease in uterine weight increased with the increase in the duration of ANT exposure. There was no effect on body weight/body-weight gain. *Vaginal opening*: None of the ANT females had an open vagina at study termination [PND 43].

Sprague-Dawley (SD) female rats: Atrazine: *Uterine growth*: Decreased uterine weight was observed at the high-dose level following exposure to atrazine from PND 22-PND 45 [24 doses]. However, statistical significance was not attained, and the magnitude of the effect [blotted 13%/dry 11% lower than control] was slight, as was the body-weight deficit [4% lower than control]. *Vaginal opening*: There was a statistically-significant delay in VO at the mid- [PND 41]

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and high-dose [PND 42] levels compared to the control [PND 39] following the PND 22-45 dosing regimen. In contrast to the AP females, a delay in vaginal opening was observed in the SD females at a dose level where uterine weight was not affected by treatment.

The NOAELis 10 mg/kg/day, based on delayed vaginal opening [SD rats] and reduced uterine growth [AP rats] at the LOAEL of 30 mg/kg/day.

This nonguideline special study on female rat sexual maturation is classified Acceptable/non-guideline.

Attachment 2: Effects of Atrazine on the First Spontaneous Ovulation of Female SD Rats Administered Pregnant Mare's Serum Gonadotropin [PMSG] on PND 30.

In a special study [MRID 45711303] undertaken to determine the doses of atrazine necessary to disrupt parameters of ovulation and reproductive function in peripubertal Sprague-Dawley female rats, groups [ranging from 24-42 rats] of Sprague-Dawley (SD) female rats were dosed once daily [PND 30 to PND 32] *via* gavage [10 mL/kg] with atrazine [98.2%; 1, 5, 10, 50, 100, 300, 500 mg/kg/day] or vehicle [67 rats; carboxymethylcellulose (CMC)] following a subcutaneous injection of an extract of pregnant mare's serum gonadotropin [PMSG] on PND 30.

Body weight was not adversely affected at any dose level. Decreased body-weight gains [PND 30-32] were observed at dose levels of 50 mg/kg/day [80% of control] and above [67%-72% of control]. There was a decrease in the % of females with ova [% ovulation] at the 100 mg/kg/day [60%] and 500 mg/kg/day [54%] dose levels but not at 300 mg/kg/day or at the 1-50 mg/kg/day dose levels. Of the females that did ovulate, there were fewer ova in those females at 500 mg/kg/day than in the control and other dose groups. Since the study was performed over a 16-week period, there were limited time points that were common between control and treated groups. Data are available for comparison of the % ovulating and number of ova for weeks 14 and 15 for the control and the three highest dose groups. This comparison shows a dose-related decrease in the number of ova in those females that ovulated, but the % of females that ovulated was lowest in the control group. Due to the question of whether atrazine was dosed during the critical period to demonstrate an effect on ovulation, no conclusion regarding the apparent lack of an effect at lower dose levels can be made.

The study lacks performance criteria. The control group showed the lowest ovulation rate for 7 of the 14 weeks in which a control group was run. Additionally, the percent of control female groups displaying greater than or equal to 50% ovulation is 57% compared to 100% in all but the 100 mg/kg/day dose group [71%]. Based on this, the failure to demonstrate the capability to consistently induce ovulation in the immature female control rat with the model utilized, and the questionable timing of treatment, no definitive conclusion regarding the effect of atrazine on ovulation in the immature female rat is possible.

For body-weight effects, the NOAEL is 10 mg/kg/day, based on decreased body-weight gain at the LOAEL of 50 mg/kg/day. Although inhibition of ovulation and a decreased number of ova in those females that ovulated were observed at 500 mg/kg/day compared to the control, *no definitive LOAEL/NOAEL can be determined.* This is due to the fact that there are no data to support the selected time [10 am to 12 noon] when the dose of atrazine was administered, and the lack of an effect at lower dose levels may have resulted because exposure to atrazine did not occur during the critical period. Lack of a positive control and a failure to demonstrate the capability to consistently induce the immature female control rat to ovulate with the model used added difficulty to the interpretation of the data.

This nonguideline special study on female rat sexual maturation is classified Unacceptable/non-guideline. The study is unacceptable based on the questionable timing of the atrazine dose and the failure to demonstrate the capability to consistently induce ovulation in the immature female control rat with the model utilized.

Attachment 3: Dietary Exposure and Tolerance Reassessment Comments

Comment 1
Syngenta has reviewed the acute and chronic dietary risk assessments contained in the revised human health risk assessment, and agrees with the conclusions stated in the document. They respectfully conclude that no further refinements are necessary.

HED Response
HED has no further comment.

Comment 2
Syngenta agrees to HED's proposal to lower tolerances for residues of atrazine and the chlorinated metabolites on wheat fodder to 1.5 ppm, grain to 0.10 ppm, and straw to 0.50 ppm.

HED Response
HED has no further comment.

Comment 3
Syngenta respectfully requests lowering the reassessed tolerance for milk to 0.02 ppm for atrazine and the chlorinated degradates once they have amended labels to reflect a 45-day PHI for post-emergent use on sweet corn.

HED Response
In the April 16, 2002 response to comment document, HED recalculated the MTDB for dairy cows based on the proposed sweet corn forage tolerance of 1.5 ppm reflecting a 45-day PHI for post-emergence treatments, and estimated a tolerance for atrazine and the chlorinated degradates of 0.03 ppm in milk. Syngenta's recalculation results in an estimated milk tolerance of 0.02 ppm. HED's recalculation estimated a MTDB of 2.0 ppm and extrapolated from residues found

at the 3.75 ppm feeding level. Total chlorinated residues were summed to <0.06 ppm (<0.01 ppm atrazine, < 0.01 ppm des-ethylatrazine, < 0.01 ppm des-isopropyl atrazine, and <0.01-0.03 ppm DACT) at the 3.75 ppm feeding level. Extrapolating from 3.75 to 2 ppm, residues would be expected to be ~ 0.032 ppm. Using the same approach, total chlorinated residues were summed to <0.47 ppm (0.01 ppm atrazine, < 0.01- 0.03 ppm des-ethylatrazine, < 0.01 - 0.02 ppm des-isopropyl atrazine, and <0.20-0.41 ppm DACT) at the 37.5 ppm feeding level. Extrapolating from 37.5 to 2 ppm, residues would be expected to be ~ 0.025 ppm. HED respectfully confirms that for the purposes of tolerance setting, total chlorinated atrazine residues are expected not to exceed 0.025 to 0.032 ppm., and recommends the milk tolerance for atrazine and the chlorinated degradates be established at 0.03 ppm once the registrant makes the appropriate label amendments to reflect a 45-day PHI for post-emergent application of atrazine to sweet corn. HED cannot recommend for a tolerance representing the legal limit for total chlorotriazine residues below the high-end of anticipated levels.

Comment 4

Syngenta agrees to HED's proposal to establish a tolerance of 5 ppm for residues of atrazine and the chlorinated metabolites on wheat hay based on anticipated concentration of residues in wheat forage.

HED Response
HED has no further comment.

Comment 5
Syngenta agrees to HED's requirement for an additional sugarcane processing study to establish the need for a separate tolerance in molasses. They also agree to analyze the molasses for atrazine, the chloro- and hydroxy-metabolites. They intend to conduct a guideline study once the RED is finalized.

HED Response
HED has no further comment.

Comment 6
Syngenta does not wish to support a crop group tolerance for Crop Group 17 (Grass, Forage, Fodder, and Hay).

HED Response
HED recommends that the tolerance of 4 ppm on *Grasses, range* be revoked and uses cancelled.

Comment 7
Syngenta respectfully requests that HED reconsider the requirement for tolerances for the hydroxy-metabolites of atrazine on corn and sorghum forage, fodder, and silage, and wheat forage, straw, and hay. Syngenta believes that as HED does not expect finite residues in animal

commodities, the need for tolerances in animal feeds is moot. Further, since there are tolerances for atrazine and the chlorinated metabolites in animal feed commodities, illegal and misuses of atrazine products, if occurring will be detected. Syngenta believes the additional tolerances on hydroxy metabolites are an unnecessary duplication of enforcement requirements.

HED Response
HED will reconsider this issue and seek resolution at the HED Metabolism Assessment Review Committee (MARC). The Committee's decision will be reflected in the Interim Reregistration Eligibility Decision (IRED) for atrazine.

Comment 8
See comment 3.

Comment 9
Syngenta agrees to conduct additional storage stability data as required in the revised human health risk assessment on atrazine and the chloro-metabolites in sugarcane, wheat, and processed commodities from corn and sorghum once the RED is finalized.

HED Response
HED has no further comment.

Comment 10
Syngenta does not wish to support the existing tolerance on *Grasses, range*.

HED Response
HED recommends that the tolerance of 4 ppm on *Grasses, range* be revoked and uses cancelled.

Attachment 4: Occupational and Residential Exposure Assessments

EPA has put a considerable amount time and effort into revisions of the atrazine occupational and residential exposure (ORE) assessment. Syngenta appreciates that the additional agronomic practices and atrazine use and usage information obtained from various sources were considered for incorporation into the risk assessment. The revised residential risk tables clearly present the data by formulation and provide detailed explanation.

Comment (page 29 of revised ORE assessment), EPA comment: Because several of the short-term residential exposures exceed EPA's level of concern, no short-term aggregate FQPA risk assessment was conducted.

Syngenta response: According to the residential risk assessment conducted by HED, the risks for homeowners and children exposed to the granular formulation are acceptable and do not exceed EPA's level of concern. On page 113, a short-term aggregate FQPA risk assessment was successfully conducted for adults. On page 115, it was noted that the residential aggregated risks

for children and infants was acceptable within MOE of 730. Based on this, it appears that a short-term aggregate risk assessment could be conducted for at least the granular formulation.

HED Response
The statement made in the document will be modified to reflect the fact that the short-term aggregate risk assessment was conducted for some scenarios which did not have a risk of concern from a single pathway. Please refer to the memorandum entitled, "Atrazine: Addendum to Revised Human Health Risk Assessment for the Reregistration Eligibility Decision (RED)" (DP Barcode: D287740) for details on the short-term aggregate risk assessments, dated January 31, 2003.

Comment (page 30 of revised ORE assessment), EPA comment: The dry fertilizer admixture (mixer/loader)scenarios exceeded the level of concern for the highest estimated daily quantities handled.

Syngenta response: The most critical variable in the risk calculation for fertilizer impregnation workers is the assumption of how many tons of fertilizer they will treat with atrazine in a day. Information obtained by Syngenta from fertilizer dealerships indicate that the EPA's assumption that 960 tons of fertilizer per day can be treated with atrazine is a gross overestimate. The actual figure is closer to 200 tons per day, approximately four times less than the value used by EPA. This information was provided to EPA during a previous comment period(MRID # 45399905, April, 2001). The impregnation of 200 tons of fertilizer with atrazine results in risks to workers that do not exceed EPA's level of concern.

HED Response
Based on all of the information available to the HED, including conversations with agricultural experts, the figure of 960 tons of fertilizer admixture represents a maximum quantity based on technical feasibility, for the purpose of determining short-term exposure; 500 tons of fertilizer admixture per day is the practical maximum quantity according to Syngenta documentation; and 200 tons of fertilizer admixture with atrazine could be considered as a "typical" daily quantity. The policy of the HED in conducting exposure assessment is to follow the maximum label rates and the highest practical acreage to determine exposure. "Typical" rates and acreages are generally only employed in determination of chronic exposures and cancer risks. However, since the technical maximum may be unrealistic for intermediate term exposures, the Syngenta value of 500 tons per day will be assumed to be realistic for intermediate-term exposure assessments, which will be reflected in the revised assessment.

Comment (page 30 of revised ORE assessment), EPA comment: There were no exposure data for liquid/liquidfertilizer treatment, so risk estimates for this scenario could not be calculated.

Syngenta response: The physical process of mixing/loading liquid atrazine into a tank containing liquid fertilizer is equivalent to the mixing/loading of a liquid pesticide into a spray tank containing water, a scenario adequately covered by data in PHED. Therefore, sub setting PHED

for open mixing/loading of liquids and closed mixing/loading of liquids would provide adequate data for assessing risks to fertilizer treatment workers. This use of mixing/loading liquid pesticides for spraying operations as surrogate for liquid/liquid fertilizer treatment has been proposed by the technical committee of the new industry Agricultural handler's Exposure Task Force (AHETF) and will be discussed in future meetings with the Joint Regulatory committee members.

HED Response
The EPA statement is misleading, as PHED data for open and closed mixing and loading were used to estimate the exposure and risk for liquid/liquid fertilizer treatment.

Comment (page 31 of revised ORE assessment), EPA comment: Intermediate-term exposures that exceed HED's level of concern are generally associated with mixing and loading of the higher application rates and acreage for use on chemical fallow lands, grasslands, corn, sorghum, and in fertilizer admixture.

Syngenta response: This statement is erroneous as it is based on some incorrect data presented in Table 8 (page 33) of the ATRAZINE: Revised occupational and Residential Exposure Assessment and recommendations for the Reregistration Eligibility Decision Document, dated April 25, 2002. Table 8 summarizes data presented in Tables 5, 6, and 7. The intermediate-term MOEs for scenario 1a (mixing/loading liquid formulations for aerial applications) and scenario 2a (mixing/loading dry flowable (WDG) for aerial) with the upper-bound daily acreage (1,200acres) are correctly indicated as "na" in Tables 6 and 7; however, these"na" designations did not get copied into Table 8.As discussed in HED's April 16, 2002, response to Syngenta's comments(page 38), neither the upper-bound daily aerial acreage (1,200 acres) nor the upper-bound daily ground acreage (450 acres) are appropriate for intermediate-term exposure calculations. This is also re-iterated on page29 of the April 25, 2002 Revised Occupational and Residential Exposure assessment and Recommendations for the Reregistration Eligibility decision for atrazine. However, Table 8 has MOEs using these upper bound acreage values and needs to be corrected. This will, in turn, change the conclusion regarding acceptable intermediate-term risks. Based on HED's statement that neither the maximum daily aerial or ground acreage will be used for intermediate-term risk assessments (seepage 38 of HED's April 16, 2002 response to Syngenta's comments), it appears that scenarios 1b and 2b need to be revised in Tables 5, 6, 7, and 8. As a result of these revisions, all intermediate-term risks for mixer/loaders become acceptable with either the use of personal protective equipment or engineering controls. Similar logic should be applied to the dry bulk fertilizer impregnation scenario. A typical value (i.e. 200 tons/day) should be used for assessing intermediate-term risks where it is assumed a fertilizer facility worker would treat with atrazine for a period of 30 days to 6 months.

HED Response
The HED agrees that adequate data were presented by the NAAA and Syngenta, and confirmed by BEAD, which indicate atrazine is predominantly sprayed by groundboom equipment, and the

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large aerial applications would not exceed 30 days per season. Those table rows which contained the higher aerial acreage for intermediate term have been removed from the occupational exposure assessment and the risk assessment will be updated to reflect the change. For ground application, daily acreage treated information was obtained from several different surveys. These data support typical daily treatment of 150-200 acres and a maximum of about 500-600 acres. Therefore, the HED has determined that it is also unlikely any single person would mix/load or apply atrazine to more than 200 acres by ground spray over more than 30 days. The atrazine risk assessment will be updated to reflect this determination. Table 14 in the human health risk assessment will be replaced with the corrected values and notations in Table 8 of the ORE chapter. Please refer to the memorandum entitled, "Atrazine: Addendum to Revised Human Health Risk Assessment for the Reregistration Eligibility Decision (RED)" (DP Barcode: D287740, dated January 31, 2003) for Table 8.

Comment (page 106 of revised ORE assessment), EPA comment: A single label for atrazine 4L (EPA Reg No.829-268) permits professional application to "corn in the home garden".

Syngenta response: This paragraph should be removed. As acknowledged in HED's April 16, 2002 response to Syngenta's comments(page 33), the newest label for this product (EPA Reg No 829-268accepted 10-28-96) does not have the home corn use. Therefore, this use will be removed from the revised risk assessment. Syngenta's products containing atrazine do not allow use on corn in the home garden and we are unaware of any other current labels allowing this use.

HED Response
The change has been made in the Occupational and Residential Exposure chapter and has been made to the human health risk assessment. Please refer to the memorandum entitled, "Atrazine: Addendum to Revised Human Health Risk Assessment for the Reregistration Eligibility Decision (RED)" (DP Barcode: D287740, dated January 31, 2003).

Comment (page 122 of revised ORE assessment), EPA comment: Only the right-of-way scenario had a MOE less than 100 (37) with added PPE but had no known engineering exposure control method.

Syngenta response; The application method, equipment, and use pattern for the right-of-way scenario are not specified in the ATRAZINE: Revised Occupational and Residential Exposure Assessment and recommendations for the Reregistration Eligibility Decision Document, dated April 25, 2002. Thus it is not clear how the dermal and inhalation values for the right-of-way application scenario in Table 6 are derived from PHED. These values are significantly different from the roadside scenario. It would be helpful if the parameters used to subset PHED for right-of-way application were specified.

HED Response
The atrazine exposure assessment for spraying rights-of-way (ROW) used the PHED data which were based on a study of hand-spraying ROW, for example, around utility poles. Atrazine is

labeled for roadside ROWs, which are commonly sprayed from a truck or other vehicle. The PHED data may not be applicable for truck-mounted boom spraying operations, which studies indicate have lower unit exposures than hand methods. If atrazine labeling restricted ROW uses to truck-mounted boom type sprays, or other remotely controlled methods, lower risks would be anticipated. Some data are available from a California Department of Pesticide Regulation, Worker Health and Safety Report (HS-1700, 1995) which measured CalTrans utility workers spraying simazine on rights-of-way. Both truck-mounted boom spraying and hand held spraying from a truck cab were used. Passive dosimetry and urinalysis biomonitoring of exposure were performed. The study results were compared to exposure estimates based on equivalent PPE levels in PHED (although PHED assumes a 50% protection factor for cloth coveralls, and the study participants generally wore Tyvek coveralls during mixing and loading and application). Using the same amount of chemical handled, the daily exposure estimates from the study were generally lower than estimates using comparable unit exposures from PHED. In the CalTrans study most handlers were mixer/loader/applicators. The highest dermal exposure by passive dosimetry was 5.6 mg simazine/person/day and the highest internal dose was 16 ug simazine mercapturate for the same handler, mixing, loading, and applying using both boom and hand spray from the cab. This person handled only 27 lb of simazine on that day, yet had lower exposures on days when he/she handled more simazine. Two other volunteers performing the same work and handling about 50 lbs simazine had two to four times *lower* exposures. The report states that little to no statistical correlation was found between the quantity of ai handled by job category and the exposure received. Using the average dermal exposure from the simazine study for the highest-exposure work category (mixing/loading/applying via boom and spray from the cab), a unit exposure of 0.043 mg/lb ai handled is obtained. The PHED ROW *sprayer only* dermal unit exposure with coveralls and gloves is 0.29 mg/lb ai handled. The investigators for the California ROW study characterized their methodology as representing realistic exposures since workers performed their jobs as they normally would, without direction from the observers; they wore their usual PPE, and the work practices were described in some instances as unusually sloppy, resulting in obvious contamination. Therefore, the California study results, while not completely comparable to the PHED estimates, imply that for truck-mounted applications, for a similar chemical (simazine), for mixer/loader/applicators with full PPE, exposures on average were several times lower than estimated using PHED data for ROW hand application. The California ROW study also recommended that hand spraying from the cab be eliminated as it caused by far the highest exposure.

Comment (page 123 of revised ORE assessment), Table 14

Syngenta response: There are some errors in this table. Intermediate-term risks should be calculated with the typical acreage values only, not using the upper-bound acreage values (1,200 acres for aerial and 450acres for ground). See comment 4 for further explanation.

HED Response
See response to Comment 4.

Comment (page 99 of revised ORE assessment), EPA comment: (2) mixing, loading, and applying liquid and wettable powder formulations with a low pressure hand wand.

Syngenta response: To our knowledge, there is no wettable powder formulation sold to homeowners.

HED Response
This scenario has been removed from the risk assessment. Please refer to the memorandum entitled, "Atrazine: Addendum to Revised Human Health Risk Assessment for the Reregistration Eligibility Decision (RED)" (DP Barcode: D287740, dated January 31, 2003).

Comment (page 105 of revised ORE assessment): EPA comment: However, both the short-term dermal (for the spray-treated turf) and short-term hand-to-mouth exposures have MOEs less than 1000. Data from a hand press study of dermal transfer from turf treated with granular formulations of atrazine were used to estimate hand-to-mouth exposure for children on granular-treated turf. These risk estimates indicate risks of concern for each route until residues of atrazine have declined or dry after treatment.

Syngenta response: The reference to the MOEs being less than 1000 should be changed to less than 300 as 300 is the critical safety factor. Since the data from the hand press study conducted on turf treated with granular product showed the children's hand-to-mouth ingestion risk to be acceptable, the last sentence is misleading. It appears that the last sentence is actually referencing the dermal and hand-to-mouth exposures following a liquid spray treatment to the turf and not the granular formulation.

HED Response
The MOE reference will be corrected to read 300.

Part II

Comments on HED's April 25, 2002: ATRAZINE: Revised Occupational and residential Exposure Assessment and Recommendations for there registration Eligibility Decision Document

Comment. (Page 4) EPA comment: Engineering controls raise most of the total MOEs above 100, except mixing/loading of the largest quantities (dry flowable/WDG) of chemical handled fo r the highest acreage and mixing/loading liquids for fertilizer admixture.

Syngenta response: This statement regarding large quantities of chemical is based on erroneous information in Table 8. Intermediate-term risks should have been calculated using the typical acreage values only, not using the upper-bound acreage values (1,200 acres for aerial and 450 acres for ground). See comment 4 in the previous section for further explanation. When using the correct parameters, the risks to mixer/loaders are acceptable.

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HED Response
See response to Section 1, Comment 4.

Comment (Page 24) EPA comment: (in reference to a submitted Syngenta worker exposure monitoring study) Also, due to collection of 24 hour urine samples during the spray season, it was not possible to determine the relationship between the amount handled on a given day and the chlorotriazines excreted the following day.

Syngenta response: The purpose of this monitoring study was to measure the actual absorbed dose that commercial applicators and farmers were being exposed to while performing their regular job functions during the atrazine spray season. Although monitoring workers under controlled conditions provides a good way to correlate amount of chemical handled with dose which can then be plugged into exposure calculations using default assumptions, situational biomonitoring, such as was done in this study, allows researchers to monitor how much chemical workers are actually being exposed to under real-life conditions. No default assumptions regarding "typical" or "upper-bound" acreage treated or gallons handled are needed with this type of monitoring.

HED Response
The exposure assessment clearly stated that the biomonitoring was useful to compare to the scenario-based exposure estimates. However, it is difficult to directly compare exposure estimates based on quantities of atrazine handled with the accumulated dose based on several days' exposure. Another value of the "real-life" monitoring was to show that no person in the study incurred a dose that exceeded HED's level of concern.

Comment (Page 33), EPA comment: The baseline scenario generally represents handler wearing long pants, a long-sleeved shirt, and no chemical resistant gloves.

Syngenta response: This exposure scenario is based on workers wearing less than the Federally mandated personal protection equipment as established by the Worker Protection Standards. The wearing of protective gloves is a requirement for all handlers mixing and loading agricultural pesticides, even with the least toxic products.

HED Response
The 40 Code of Federal Regulations (CFR) Part 170, the Worker Protection Standard (WPS), does not specify that all pesticide handlers must wear protective gloves. The WPS does state that the protective equipment to be worn is based on the specific label. However, the Labeling Manual published by the Office of Pesticides to guide the creation of labels requires that mixer/loaders of any toxicity Category I, II, or III products wear protective gloves. This does not include "the least toxic products." The HED estimates exposures based on standard handler scenarios, standard suites of clothing and protective equipment and engineering controls. This standardizes exposure assessments and allows the current and future risk assessors and risk managers the greatest flexibility in decision making.

Comment (Page 33), EPA comment: The short term exposure assessment does not require the use of a dermal absorption factor since the toxicity endpoint is based on a 21 day dermal study.

Syngenta response: This statement is no longer correct. The short-term dermal endpoint in the draft RED was from the 21-day dermal toxicity study; however, at the April 2002 Atrazine Technical Briefing, a new set of short-term toxicological endpoints were disclosed. Syngenta disagrees with the use of the new endpoint for occupational exposure assessments(see Mammalian Toxicology section of this response). The new short-term dermal endpoint was from an oral study and, thus, the dermal absorption factor of 6% was utilized.

HED Response
This statement is noted as incorrect in the ORE chapter, and has been corrected in the memorandum entitled, "Atrazine: Addendum to the Revised Occupational and Residential Exposure Assessment and Recommendations for the Reregistration Eligibility Decision Document" (DP Barcode: D287742, dated January 31, 2003).

Comment (Page 38), EPA comment: PHED unit exposure values are not available for using liquid formulations to impregnate liquid or dry bulk fertilizer.

Syngenta response: As noted previously, the physical process of pouring liquid atrazine into a tank containing liquid fertilizer is equivalent to the mixing/loading of a liquid pesticide into a spray tank containing water, a scenario adequately covered by data in PHED. It would seem that sub setting PHED for open mixing/loading of liquids and closed mixing/loading of liquids would provide adequate data for assessing risks to liquid fertilizer treatment workers. This use of mixing/loading liquid pesticides for spraying operations as surrogate for liquid/liquid fertilizer treatment has been proposed by the technical committee of the new industry Agricultural Handler's Exposure Task Force (AHETF), of which Syngenta is a member, and will be discussed in future meetings with the Joint Regulatory committee members which include EPA, DPR and PMRA.

HED Response
The exposure assessment goes on to say in the same sentence:
"therefore, closed system engineering control values for mixing and loading liquids were used as a surrogate for commercial operations. For comparison, the Helix™ seed treatment study exposure data were also used, which provided slightly lower risk estimates."

Comment Tables 5, 6, 7 and 8: Intermediate-term risk estimates for mixer/loaders and applicators.

Syngenta comment: Some intermediate-term risk estimates were conducted using the typical acreage only, not the upper-bound estimates, while other estimates were done using the upper-bound estimates of1,200 acres per day by air and 450 acres per day by ground. Use data by state and farm size data previously submitted to the agency showed that the assumption of one

worker handling and/or spraying the upper-bound acreages for more than 30 days per year is not realistic. As stated in HED's April 16, 2002, response to Syngenta's comments on page 38,neither the upper-bound daily aerial acreage (1,200 acres) nor the upper bound daily ground acreage (450 acres) are appropriate for intermediate-term exposure calculations. This is also re-iterated on page 29 of this document. These tables need to be corrected.

HED Response
See response to Section I, Comment 4.

Attachment 5: Occurrence of Atrazine in Community Water Systems on Groundwater and Rural Wells in High Atrazine Use Areas

Comment

Syngenta provides comment on the portion of the human health risk assessment addressing exposures to total chlorotriazines in CWS sourced by groundwater, and rural drinking water wells. Syngenta agrees with the overall conclusion drawn in the risk assessment regarding CWS using groundwater, but believes the data were not used appropriately. Syngenta also provides a rationale as to why there are likely to be ~30 rural drinking water wells with concentrations of chlorotriaizines greater than 12.5 ppb.

HED Response

HED acknowledges Syngenta's agreement with the general conclusion in the risk assessment that atrazine use does not impact CWS using groundwater as heavily as it does rural wells and CWS using surface water, and that HED has the least concern for exposures through these CWS.

[HED defers to EFED on Syngenta's agreement with the statement that exposures to chlorotriazines in CWS using groundwater are "low and limited" taken from EFED memorandum dated April 9, 2002, "Response to Comments Contained in Attachment 6 of Syngenta's Comments on "Atrazine: HED's Revised Human Health Risk Assessment for the Reregistration Eligibility Document (RED)".]

[HED also defers to EFED for a response as to how the data on CWS using groundwater were used in that memorandum, and on their rationale regarding the number of rural wells with concentrations of chlorotriazines greater than 12.5 ppb.]

Attachment 6: "Effect of time Trends in Total Chlorotriazine Residue concentrations on the Probabilistic Assessment of Drinking Water and dietary Exposure Combined Using Water concentration Data Between 1993 and 2001 (Amendment 2 *to* MRID 45622307)".

Comment

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Syngenta provided an assessment of atrazine exposures over the period 1993 to 2001 at the 30 CWS assessed probabilistically. They state that exposures are decreasing over time. They state that most CWS that exceed levels of concern, do so before 1998. They conclude that probabilistic analyses for the CWS should have been conducted with data from the last 3 to 5 years only.

HED Response

HED acknowledges all of the work Syngenta has done to assess decreasing trends of concentrations of and exposures to atrazine over the period 1993 to 2001 in the ~30 CWS with risks above levels of concern. HED agrees with Syngenta that for these ~ 30 CWS, the majority of them show exposures above levels of concern for the earlier years between 1993 and 2001. HED defers comment on the trend analysis to EFED. Their response to the trend analyses is given under Attachments 7 & 8 below.

Any decreasing trends in concentration and exposure in these CWS may be attributed to reductions in rate, best management practices, and/or increasing treatment with powdered activated carbon (PAC) for these CWS. Reductions in rate were effective in 1992. Since most CWS that exceed levels of concern, do so before 1998, but after 1992 when data on atrazine in drinking water became available, and atrazine use has continued to rise on a volume basis, it is unlikely that the decreasing trends are completely because of those rate reductions. Also, it is possible that a combination of rate reductions, BMPs, and increased treatment with PAC have resulted in decreasing trends of concentration and exposure at these CWS. HED also notes that increased PAC treatment at the ~30 CWS assessed probabilistically is likely since these CWS are some of the most contaminated. Increasing treatment to reduce exposure passes the cost of clean water on to the consumer. It would be interesting if Syngenta researched the use of PAC over time at the ~ 30 CWS, and whether it has increased between 1993 and 2001.

Probabilistic assessments are conducted to utilize all available information on exposure in a way that provides the most variety of possible outcomes. Given the small number of CWS with sufficient data to analyze probabilistically and HED's belief that these ~30 CWS represented high-end exposures to atrazine in the US, HED elected to analyze the available data on atrazine in the ~30 CWS to maximize variability in the exposure assessment rather than to analyze the data in such a way that trends over time could be discerned. HED's intent was to assess as many of the possible exposures as the data allowed. To truncate the data set and use on 1998 through 2001 would have deleted 4 to 5 years of data. Since the purpose in conducting probabilistic assessments is to maximize variability as stated this approach seems to defeat the intent of the assessment. However, HED understands that rate changes made in 1993 and 1994 impacting surface water concerns would not have been reflected until post 1994, and that data from 1995 or 1996 on may be more representative of current use patterns and agricultural practices.

Attachments 7 & 8: "Atrazine- Overview Report - An Analysis of the Trends in Total Chlorotriazine Concentration in Raw and Finished Drinking Water in High Atrazine Use Areas (MRID 45622307)", and "Analysis of Total Time Trends in Total Chlorotriazine

Residue Concentrations in Finished Drinking Water in 28 Community Water Supply Systems Between 1993 and 2001" (Amendment 1 to MRID 45622307)".

Comment

Syngenta submitted the report "Atrazine: Overview, An Analysis of the Trends in Atrazine Concentration in Raw and Finished Drinking Water in High Atrazine Use Areas" to show this declining trend in concentrations of atrazine in midwestern bodies of water. This report included two amendments containing time trend analyses, Amendment 1 focused on total chlorotriazine concentrations over time for 28 CWSs designated as high atrazine use areas and Amendment 2 focused on the effects of time trends on a probabilistic assessment of total chlorotriazine exposure in infant subpopulations for each of the 28 CWSs. Amendment 2 is discussed above under Attachment 6. SERA (contractor to EFED) reviewed the appropriateness of the statistical analyses and attempted to reproduce all results reported in the study. The Overview Report and Amendment 1 are discussed below.

EFED Response

The Atrazine: Overview Report presents the results of a linear regression model testing decreasing trends of total chlorotriazine concentrations in raw water for 62 CWSs from 1993 to 2001 (length of study varies for individual CWSs). Linear regression models are fit to the data with atrazine concentration as the response variable and time as the explanatory variable. Assuming that this is the appropriate form of the model, the intercept would be interpreted as the mean atrazine concentration at time zero and the slope would be interpreted as the change in the atrazine concentration per unit time. The choice of a straight line is reasonable for the short time period of the study (7.5 years) but it would not be expected to hold over a longer period of time if the slope is negative, as the concentration would eventually reach zero. This is not a reasonable expectation, particularly for high atrazine use areas.

The "Trend" referred to in the table entitled " Temporal Trends in Raw Water for CWS in VMP with a Minimum of 5 years of Monitoring Data" is the estimated slope of the regression model. What is meant by "significant" in that table is that the estimate of the slope obtained from the data is of sufficient magnitude that the null hypothesis that the true (but unknown) slope is exactly zero can be rejected. The level of significance used in Table 1 is $\alpha = 0.10$. This is a relatively large α; for example, if the 62 tests are independent one would expect to find an estimated slope to be significantly different from zero approximately 6.2 times on average. The appropriate α level is 0.05; thus the number of significant trends is inflated. Table 1 does not provide strong support for the conclusion that the concentration of atrazine shows a generally negative trend. For nearly 63% (or 39/62) of the CWSs, the data indicates either no change in the concentration or an increase in the concentration. Reevaluating the data with $\alpha = 0.05$ or 0.01 would likely result in even fewer indications of a negative trend.
It would be helpful to see some indication of the degree to which the linear model fits the data. It is customary to provide this information by reporting the coefficient of determination (r^2). This

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index would be interpreted as the fraction of the variability in atrazine concentration that is explained by the explanatory variable time.

Amendment 1 provides an analysis of time trends in total chlorotriazine concentrations in finished (treated) water from 1993 to 2001 was conducted for 28 CWSs with high atrazine use . The large number of negative slopes does appear to support the claim that the atrazine concentration is generally declining for the 28 CWSs selected to be representative of vulnerable CWSs in high atrazine use areas. However, r^2 values or other indicators of goodness of fit of these linear regressions were not reported in the amendment, making it difficult to evaluate the validity of this conclusion. SERA reproduced the linear regressions reported in Amendment 1 successfully for the parameters: slope, and y-intercept (see the attached Table on next page). Although the coefficient of determination was not reported in the Amendment it was calculated by the Agency's reviewers. SERA successfully reproduced these values but it is important to note the low r^2 values with a mean of 0.09 and a single maximum r^2 of 0.29. Thus, while many of the regressions show a significant negative trend, the degree to which the trend fits the data is poor. These results are shown in the table below.

It is important to note that as stated in the response to Attachment 6, any decreasing trends may not be entirely to decreasing concentrations of chlorotriazines. The impact of any increase in treatment with PAC has not been considered in the analysis.

Syngenta						SERA		
Intercept	Slope	p-Value	p-Value	R^2	PWS - ID	Intercept	Slope	R_2
6.00	-0.0015	3.81E-89	<0.0001**		Regression All Sites Combined			
2.28	0.0000	4.19E-01	0.4189		Regression for IA5903011	2.23	0.0001	
5.43	-0.0012	2.24E-07	<0.0001**		Regression for IL0050300	5.43	-0.0012	
4.37	-0.0003	2.22E-01	0.2217		Regression for IL0250100	4.35	-0.0008	
6.52	-0.0014	4.98E-07	<0.0001**		Regression for IL0470200	6.52	-0.0014	
5.94	-0.0008	5.61E-06	<0.0001**		Regression for IL0510150	5.94	-0.0009	
1.25	0.0052	3.64E-08	<0.0001**		Regression for IL0610400	0.25	0.0052	
4.24	-0.0009	3.75E-08	<0.0001**		Regression for IL1170150	4.24	-0.0009	
3.79	0.0028	3.65E-05	<0.0001**		Regression for IL1170400	3.79	0.0028	
11.54	-0.0016	6.81E-03	0.0068		Regression for IL1170500	11.52	-0.0016	
4.61	-0.0007	3.88E-03	0.0039		Regression for IL1170950	4.60	-0.0007	
9.60	-0.0024	1.09E-31	<0.0001**		Regression for IL1175150	9.60	-0.0024	
5.15	-0.0010	3.63E-15	<0.0001**		Regression for IL1175200	5.15	-0.0010	
2.22	-0.0012	2.53E-08	<0.0001**		Regression for IL1210300	2.23	-0.0012	
10.00	-0.0038	1.82E-12	<0.0001**		Regression for IL1210450	10.01	-0.0038	
4.04	-0.0007	7.22E-03	0.0072		Regression for IL1214220	4.04	-0.0007	
5.10	-0.0017	2.50E-06	<0.0001**		Regression for IL1350300	5.10	-0.0017	
2.45	-0.0007	1.54E-10	<0.0001**		Regression for IL1910450	2.45	-0.0007	
2.48	-0.0006	4.04E-01	0.4036		Regression for IL0250200	2.48	-0.0006	
5.93	-0.0032	1.16E-16	<0.0001**		Regression for IN5219006	5.90	-0.0032	
6.48	-0.0017	1.58E-01	0.1584		Regression for IN5240008	6.48	-0.0009	
						Mean R^2	0.0958	
						Std Dev	0.0787	

Attachment 9: Probabilistic Risk Assessment using Calandex™ for 11 Additional CWS

Syngenta submitted a probabilistic exposure assessment for 11 additional community water systems (CWS) identified in the revised human health risk assessment (April 16, 2002). The exposure assessment was conducted using the same exposure model and methodology as used in the revised human health risk assessment as discussed in Appendix II of that document. For details on how this assessment was conducted please refer to Appendix II of the revised human health risk assessment.

Of the 11 CWS included in this assessment, 7 were identified in the revised risk assessment with potential to exceed levels of concern, i.e., 90-day average concentration of chlorotriazines of 12.5 ppb based on quarterly maximum value of 12.5 ppb or greater as obtained from compliance monitoring data (PLEX database). The additional 4 CWS were identified with potential to exceed levels of concern, i.e., 90-day average concentration of chlorotriazines of 12.5 ppb based on a screening-level deterministic assessment. Probabilistic exposure assessments were not conducted for these 11 CWS in the revised document dated April 16, 2002.

The results of that assessment are presented below.

Results of Risk Analysis of Syngenta's PRA for 11 CWS: Maximum 99.9th Percentile Exposure Based on a Rolling 90-Day Average and % cPAD* for Populations of Interest

CWS	Adults 13 - 50		Children 7 - 12		Children 1 - 6		Infants < 1	
	Exposure mg/kg/day	%cPAD	Exposure mg/kg/day	%cPAD	Exposure mg/kg/day	%cPAD	Exposure mg/kg/day	%cPAD
Omaha, IL[1]	0.0013	72%	0.0012	66%	0.0020	111%	0.0045	250%
Carthage, IL[1]	0.00026	14%	0.00023	13%	0.00038	21%	0.00088	49%
Fort Wayne, IN[1]	0.00034	19%	0.00028	16%	0.00048	27%	0.0012	67%
Marion, KY[2]	0.0016	89%	0.0015	83%	0.0023	128%	0.0057	317%
Lewisburg, KY[2]	0.0016	89%	0.0015	83%	0.0023	128%	0.0057	317%
Dearborn, MO[2]	0.0028	155%	0.0027	150%	0.0041	228%	0.01	555%
Drexel, MO[2]	0.00042	22%	0.00041	22%	0.00063	33%	0.0015	83%
Village of Mt. Orab, OH[1]	0.0011	62%	0.0009	52%	0.0016	89%	0.0036	200%
Village of Williamsburg, OH[1]	0.0015	83%	0.0013	72%	0.0022	122%	0.0052	289%
Clermont Co., OH[1]	0.0007	39%	0.0007	39%	0.0011	61%	0.0026	144%
Delaware, OH[1]	0.0009	50%	0.0007	39%	0.0013	72%	0.0028	155%

[1] Identified in April 16, 2002, "Atrazine. HED's Revised Human Health Risk Assessment for the Reregistration Eligibility Decision (RED)" as one of 52 additional CWS using surface water with potential to exceed levels of concern, i.e., 90-day average concentration of chlorotriazines of 12.5 ppb based on quarterly maximum value of 12.5 ppb or greater as obtained from compliance monitoring data (PLEX DATABASE).

[2] Identified in April 16, 2002, "Atrazine. HED's Revised Human Health Risk Assessment for the Reregistration Eligibility Decision (RED)" as one of four CWS using surface water with potential to exceed levels of concern, i.e., 90-day average concentration of chlorotriazines of 12.5 ppb based on a screening-level deterministic assessment.

* cPAD = 0.0018 mg/kg/day and is the chronic population adjusted dose and is used for estimating intermediate-term and chronic risks

As a result of this probabilistic exposure assessment for these additional CWS, HED has revised the number of CWS with risk estimates exceeding levels of concern. Previously, HED identified 29 CWS using surface water of concern. HED has revised that number to 34 CWS. These 34 CWS are: Shipman, Gillespie, Hettick, Salem, Palmyra-Modesto, Hillsboro, Farina, Kinmundy, ADGPTV, Carlinville, West Salem, Flora, Sorento, White Hall, Louisville, Centralia, and *Omaha* in Illinois, Chariton in Iowa, Iberville in Louisiana, Batesville, Holland, North Vernon, and Scottsburg in Indiana, Lewisburg, and Marion in Kentucky, Bucklin, Dearborn, and Vandalia in Missouri, Newark, Sardinia, *Mt. Orab, Williamsburg, Clermont, and Delaware* in Ohio.

Through this assessment, additional CWS were added to the list of CWS with risk estimates of

concern, and 1 CWS was removed from the original list. The CWS removed from the list as a result of probabilistic assessment is located in Drexel, Missouri. The CWS added to the list are italicized. Table 1 contains the names and estimated risks at the 99.9th percentile of exposure for 33 of the 34 CWS. The CWS located at Shipman is not in the table below. The town is now purchasing drinking water from another source, but the CWS is listed for potential follow-up mitigation.

Table 1. Updated Appendix II of Atrazine: Revised Human Health Risk Assessment. Risk Estimates for High Seasonal Exposures to Atrazine in Finished Drinking Water and Average Dietary Exposure @ the 99.9th Percentile of Exposure* (Calandex™)

Community Water System (City/State)	Infant's Exposure (mg/kg/day)	% cPAD	Children's Exposure (mg/kg/day)	% cPAD	Adult's Exposure (mg/kg/day)	% cPAD
Chariton, IA	0.0042	235%	0.0015	<100%	0.0011	<100%
Sorento, IL	0.0033	183%	0.0013	<100%	0.0010	<100%
Flora, IL	0.0038	211%	0.0017	<100%	0.0012	<100%
W. Salem, IL	0.0034	189%	0.0018	100%	0.0014	<100%
Farina, IL	0.0034	189%	0.0012	<100%	0.0008	<100%
White Hall, IL	0.0050	278%	0.0021	117%	0.0014	<100%
Carlinville, IL	0.0023	128%	0.0011	<100%	0.0008	<100%
Gillespie, IL	0.0099	550%	0.0040	222%	0.0031	172%
Hettick, IL	0.0098	544%	0.0040	222%	0.0031	172%
Palmyra-Modesto, IL	0.0063	350%	0.0028	155%	0.0020	111%
N. Otter Twp ADGPTV, IL	0.0034	189%	0.0015	<100%	0.0010	<100%
Kinmundy, IL	0.0027	150%	0.0011	<100%	0.0008	<100%
Salem, IL	0.0095	528%	0.0048	267%	0.0036	200%
Centralia, IL	0.0046	255%	0.0018	100%	0.0013	<100%
Hillsboro, IL	0.0049	272%	0.0021	117%	0.0015	<100%
Louisville, IL	0.0062	344%	0.0022	122%	0.0017	<100%
Holland, IN	0.0044	244%	0.0023	128%	0.0017	<100%
North Vernon, IN	0.0036	200%	0.0021	117%	0.0014	<100%
Batesville, IN	0.0047	261%	0.0020	111%	0.0014	<100%
Scottsburg, IN	0.0048	267%	0.0027	150%	0.0019	105%
Iberville, LA	0.0047	261%	0.0021	117%	0.0015	<100%

Table 1. Updated Appendix II of Atrazine: Revised Human Health Risk Assessment. Risk Estimates for High Seasonal Exposures to Atrazine in Finished Drinking Water and Average Dietary Exposure @ the 99.9th Percentile of Exposure* (Calandex™)

Community Water System (City/State)	Infant's Exposure (mg/kg/day)	% cPAD	Children's Exposure (mg/kg/day)	% cPAD	Adult's Exposure (mg/kg/day)	% cPAD
Bucklin, MO	0.0045	250%	0.0018	100%	0.0012	<100%
Vandalia, MO	0.0034	189%	0.0019	105%	0.0013	<100%
Sardinia, OH	0.012	667%	0.0055	305%	0.0037	205%
Marion, KY[2]	0.0057	317%	0.0023	128%	0.0016	<100%
Lewisburg, KY[2]	0.0057	317%	0.0023	128%	0.0016	<100%
Dearborn, MO[2]	0.01	555%	0.0041	228%	0.0028	155%
Village of Mt. Orab, OH[1]	0.0036	200%	0.0016	<100%	0.0011	<100%
Village of Williamsburg, OH[1]	0.0052	289%	0.0022	122%	0.0015	<100%
Clermont Co., OH[1]	0.0026	144%	0.0011	<100%	0.0007	<100%
Delaware, OH[1]	0.0028	155%	0.0013	<100%	0.0009	<100%
Omaha, IL[1]	0.0045	250%	0.0020	111%	0.0013	<100%
Newark, OH	0.0020	111%	0.0009	<100%	0.0006	<100%

Additional Compliance Monitoring Data

Syngenta submitted additional compliance monitoring data for several additional states not submitted or considered in the revised human health risk assessment. These data are summarized below.

Syngenta submitted compliance monitoring data on atrazine and estimates of total chlorotriazines (atrazine + desethyl atrazine, desisopropyl atrazine, and diaminochlorotriazine) as collected under the Safe Drinking Water Act (SDWA) for CWS in 10 additional states from 1993 to 1999. These 10 states are considered to have low-use of atrazine. These states are: AL, AR, CO, GA, NM, OK, SC, SD, TN, and VA. These 10 states in conjunction with the 21 states previously considered in the revised human health risk assessment represent > 99% of atrazine use. The number of CWS reporting data on atrazine in these 10 additional low-use atrazine states varied. Not all of the states provided monitoring data for each of the 7 years between 1993 and 1999. The state of VA provided data for only 1 CWS sampled one time in 1997. The number of CWS

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collecting data on atrazine decreased with time over the 7-year period. However, between 1993 and 1999, the total number of CWS collecting monitoring data on atrazine across these 10 states ranged from a low of 125 in 1999 to a high of 288 in 1993. The number of samples collected at each of these CWS ranged from 1 to 4 per year.

The maximum concentrations for total chlorotriazines for each CWS for each year of monitoring data provided were compared to 12.5 ppb. None of the samples contained concentrations of total chlorotriazines greater than or equal to 12.5 ppb. Consequently, HED did not identify any additional CWS of potential concern based on compliance monitoring data from these 10 states.

Additional compliance monitoring data were submitted for 1999 for the 21 states originally assessed in the revised human health risk assessment, and for the year 2000 for a combination of states. These data impacted the CWS identified as of potential concern in Appendix III of the human health risk assessment (4/16/02). The maximum concentrations for total chlorotriazines for each CWS for each year of monitoring data provided were compared to 12.5 ppb. Three (3) CWS had samples with concentrations of total chlorotriazines greater than or equal to 12.5 ppb. These 3 CWS have been added to the updated version of Appendix III contained in table 2.

The submitted probabilistic exposure assessment also impacted the number of CWS identified as of potential concern as contained in Appendix III of the revised human health risk assessment. As a result of the probabilistic exposure assessment on the 11 CWS, and the additional compliance monitoring data submitted, approximately 50 CWS are now considered to have the potential to exceed 12.5 ppb of chlorotriazines over a consecutive 90-day period. These 50 include CWS selling and purchasing drinking water. An updated version of Appendix III reflecting these changes is provided in table 2.

Table 2. Updated Appendix III from April 16,2002 Atrazine: Revised Human Health Risk Assessment. *Community Water Systems (CWS) with Quarterly Maximum* Concentrations of Atrazine plus Chloro-Metabolites Equal to or Greater than 12.5 ppb

Year	CWS	Concentrations (ppb)	Comment
2000	Versailles, IN	15.12	
2000	Bedford, IN	13.41	
1999	Napoleon, OH	17.35	Self
1999	Corsicana, TX	15.37	
1998	Kansas City, KS	14.42	Self
1998	Defiance, OH	13.63	Self
1998	Ayersville, OH	13.63	Purchases from Defiance
1998	Cristi Meadows Subdivision, OH	13.63	Purchases from Defiance

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Table 2. Updated Appendix III from April 16,2002 Atrazine: Revised Human Health Risk Assessment. Community Water Systems (CWS) with Quarterly Maximum Concentrations of Atrazine plus Chloro-Metabolites Equal to or Greater than 12.5 ppb

Year	CWS	Concentrations (ppb)	Comment
1998	Brunersburg, OH	13.63	Purchases from Defiance
1998	Village of Blanchester, OH	12.47	Self
1998	Glasgow, MO	15.69	Self
1998	Howard Co. PWD #2	15.69	Purchase from Glasgow
1998	Waverly, IL		Self
1997	Newark, OH	29.7	Self
1997	Lake of the Woods	18.1	Self
1997	Napoleon, OH	17.9	Self
1997	Liberty Center, OH	17.9	Purchased water from Napoleon
1997	Florida City, OH	17.9	Purchased water from Napoleon
1997	Village of Malinta, OH	17.9	Purchased water from Napoleon
1997	Aquilla Water Supply District, TX	15.13	Self
1997	Brandon-Irene Water Supply Corp. TX	15.13	Self
1997	Chatt Water Supply Corp., TX	15.13	Self
1997	Files Valley Water Corp.	15.13	Self
1997	Hill Co. Water Corp., TX	15.13	Self
1997	Milford City, TX	15.13	Self
1997	City of Bynum, TX	15.13	Self
1997	Piqua, OH	14.31	Self
1996	Napoleon, OH	14.65	Self/supplier
1996	Louisville, IL	24.3	
1996	Osawatomie, KS	17.3	
1996	Miami Co. RWD #1, KS	17.3	Purchased water from Osawatomie
1996	Miami Co. RWD #3, KS	17.3	Purchased water from Osawatomie
1996	City of Osage, KS	15.84	Self
1996	Osage Co. RWD #7, KS	15.84	Purchased from City of Osage
1996	City of Reading	15.84	Purchased from City of Osage

Table 2. Updated Appendix III from April 16,2002 Atrazine: Revised Human Health Risk Assessment. Community Water Systems (CWS) with Quarterly Maximum Concentrations of Atrazine plus Chloro-Metabolites Equal to or Greater than 12.5 ppb

Year	CWS	Concentrations (ppb)	Comment
1996	Osage Co. RWD # 6, KS	15.84	Purchased from City of Osage
1996	City of Upper Sandusky, OH	14.38	Self
1996	Keysport, IL	14.42	Self
1994	Andersen Co., RWD #2, KS	15.84	Self
1994	Keysport, IL	18.7	Self
1994	Emma, MO	14.42	Self
1994	Louisville, IL	18.7	Self
1994	Vandali, IL	13.29	Self
1994	Canton	12.71	Self
1994	Cuba, IL	12.71	Purchases from Canton
1994	Norris, IL		Purchases from Canton
1994	Dunfer, IL		Purchases from Canton
1993	Three Rivers, IN*	20.1	
1993	New Haven, IN	20.1	Purchased water from Three Rivers
1993	Sunymede, IN	20.1	Purchased water from Three Rivers

The CWS serving Three Rivers, IN was not included in the VMS databases available to HED.

Attachment 10: The Selection of Endpoints, Application of FQPA Uncertainty Factors and Risk Extrapolation at the 99.9th Percentile.

Syngenta believes that the use of the LH endpoint from a 6-month study in adult rats is not appropriate for assessing risk to the young. Additionally, Syngenta concludes that their analyses should alleviate any concerns held by EPA and remove the need for additional [10X] FQPA uncertainty factors.

Comment

Sensitivity of Young. Syngenta states that all evidence indicates that young rats are less sensitive to the neuroendocrine effects caused by atrazine than adult rats. The basis for this conclusion stems from their comparison of the NOAEL/LOAEL from studies on the young animal [those where the young were not directly dosed, two pubertal assays and two recent studies in which young rats were dosed directly] with findings in the available database on the adult animal.

HED Response

Although the NOAELs in some of the adult studies are lower than those in the young, this apparent difference between the age groups may be attributed to dose spacing and/or to a difference in dosing duration. For example, comparison of the 28-day LH surge study in the female adult rat [NOAEL of 5 mg/kg/day; LOAEL of 40 mg/kg/day] with the published pubertal study in female young rat [delayed VO NOAEL of 25 mg/kg/day ; LOAEL of 50 mg/kg/day] shows rather similar LOAELs [40 *vs* 50] for similar durations of dosing [young female 20 days]. If the dose-spacing in the adult study were similar to that in the pubertal study [2X], the NOAELs might have been similar also [20 *vs* 25]. In comparisons made by Syngenta, the 6-month study duration far exceeds any study performed in the young animal, and it is well known that doses required to produce an effect following long-duration exposure are lower than for a short-duration exposure. A comparison of the adult NOAELs/LOAELs obtained in the 6-month [1.8/3.65 mg/kg/day] and 28-day [5/40 mg/kg/day] studies illustrates this also.

Based on one of the recent studies [described above] in which immature female rats were dosed directly [**21-24 days**], the lowest NOAEL was 10 mg/kg/day, based on effects [delayed vaginal opening and reduced uterine weight] at 30 mg/kg/day. Comparison of this study with the NOAEL observed in the adult female **28-day** LH surge study [NOAEL = 5/mg/kg/day; LOAEL = 40 mg/kg/day] also **does not support the conclusion** that the young female rat is less sensitive than the adult female rat.

The second study submitted recently in support of their argument about sensitivity is unacceptable, based mainly on the questionable timing of atrazine treatment. Additionally, the authors did not demonstrate proficiency with the model used, and there is a lack of performance criteria. The control group showed the lowest ovulation rate for 7 of the 14 weeks in which a control group was run. Additionally, only 57% of the control groups displayed greater than or equal to 50% ovulation compared to 100% in all but the 100 mg/kg/day atrazine group [71%]. Based on this, the lack of a positive control, and the questionable timing of atrazine treatment, no definitive conclusion regarding differences in response between the control and treated animals or between the adult and young animals is possible.

Comment

LH Surge Inappropriate Endpoint for Young. The registrant argues that the GnRH axis is "not operative in prepubertal animals", and the role of LH remains quiescent until onset of puberty, when the brain "wakes up" and LH begins to exert its actions on sexual development and, later in life, on maintenance of reproductive function. According to Syngenta, until puberty, LH plays no role and therefore cannot be affected by atrazine. Syngenta further argues that an endpoint that is based on LH or physiological functions that depend on LH are appropriate only for the peripubertal developmental stage and adults. Prepubertal endocrine-related effects that have been reported, such as prostatitis, are considered by Syngenta to be the result of effects in the mother, not in the young animal. Syngenta states that studies with other, life-stage specific, endpoints are available and are scientifically more appropriate for assessing risk to the young. Syngenta disagrees with the Agency's use of the endpoint [LH surge attenuation and estrous cycle

disruption] from the 6-month adult study for risk assessment of the young.

The registrant also states that the prepubescent surge of LH in immature female rats initiates ovarian estradiol synthesis, the growth of the uterus, acquisition of vaginal patency [VO], and the institution of regular ovarian cyclicity. The recent study submitted was conducted to "test the equivalence in dosimetry for the effects of atrazine" in peripubertal and adult female rats. The time of dosing was designed to assess atrazine's effects on sexual development at the critical moments of GnRH/LH "awakening". Syngenta states that the results support the conclusion that the pituitary/hypothalamic axis in peripubertal female SD rats is less sensitive than in adult female SD rats, as evidenced by the lower no-effect level in the adult [1.8 mg/kg/day] than in the peripubertal [10 mg/kg/day] rat.

HED Response

As noted previously, the endpoint [LH surge attenuation and estrous cycle alterations] serves as a **surrogate** for the effect of atrazine on the hypothalamic-pituitary axis/function. The hypothalamic-pituitary axis is involved in the development of the reproductive system and its maintenance and functioning in adulthood. Additionally, the reproductive hormones **modulate the function of numerous other metabolic processes, including bone formation, and immune, CNS, and cardiovascular functions**. A potential exists for reproductive as well as developmental disruption to occur as a consequence of hypothalamic-pituitary-gonadal disturbance. As discussed in the SAP report, neurogenesis is not limited to the intrauterine period and may continue throughout the lifespan. Brain development goes at an explosive pace during the first few years of life. During that time, neurons and glia are migrating and dendrites are sprouting and are being pruned back. A three year old has fewer synapses than a two year old because of the pruning process. This pruning is tightly orchestrated and under the influence of the genes and the experiences of the child. A synaptic connection that is reinforced by experience at this time is more likely to persist. Any perturbation of CNS metabolism at this time may decrease the specificity and increase the randomness of these connections. The effect of atrazine on LH and prolactin are the result of altered GnRH output, and this is mediated by neurotransmitters, NE and DA. Prolactin is regulated by DA. Because of the rapid developmental brain changes noted above, the influence of atrazine on neurotransmitters in the hypothalamus and on GnRH may well have a differential, permanent effect on children. Therefore, altered hypothalamic-pituitary function, which can potentially broadly affect an individual's functional status, is considered relevant to humans of **all population subgroups**. With respect to the comparison of NOAEL/LOAEL in the adult 6-month study with new immature rat study, both the duration of exposure [6 months *vs* 25 days] and the endpoints monitored [LH surge attenuation and estrous cyclicity disruption *vs* delayed VO and decreased uterine weight] differ.

With regard to the use of life-stage specific endpoints for assessing risk to the young, the acute dietary [females 13-50 years of age; delay or lack of ossification of several sites in the rat developmental study; NOAEL 10/LOAEL 70] and short-term incidental oral, dermal, and inhalation [delay in preputial separation in the pubertal screening study; NOAEL 6.25/LOAEL 12.5] exposure assessments are based on effects observed in the young animal. It is recognized,

however, that the developmental toxicity study involved indirect dosing of the young animal.

It is to be noted that the 6-month study is being used for **the intermediate-term** and **long-term** risk assessments only. There are no studies in the young animal of sufficient duration with which to assess intermediate-term and long-term exposure.

Comment
Inappropriate Application of the FQPA 10X Uncertainty Factor. The registrant argues that the two, recently-submitted, studies in the prepubertal female SD rat demonstrate that the pituitary/hypothalamic axis in the peripubertal/immature rat is less sensitive than in the adult female SD rat. Syngenta also provides rationale "to remove the additional FQPA uncertainty factors". This includes (1) their argument that LH plays no role in the young animal until puberty and, therefore, cannot be affected by atrazine; (2) their determination that "a great deal of data are available that describe atrazine's NOELs during the pubertal period of development." Syngenta cites the results of the recently submitted studies on sexually immature rats, which they state support the conclusion that the hypothalamic-pituitary axis in the immature female rat is less sensitive than in the adult female. The registrant points out that the study on ovulation was "unable to demonstrate significant disruption of the ovulatory process at acute doses of 300-500 mg/kg atrazine in animals 30 days old, whereas LH attenuation can be easily demonstrated by one-tenth of this atrazine dose, when administered to animals that are 6-8 months age." Based on the above, Syngenta believes EPA should remove the additional 10-fold uncertainty factor.

HED Response
With respect to the lack of a significant response in the 30-day old female SD [peripubertal] rat following a 3-day exposure to atrazine doses of 300-500 mg/kg/day, it is to be noted that there was no attenuation of the LH surge in adult female SD [ovariectomized] rats following 3 days of exposure to 300 mg/kg/day [Toxicol. Sci. 53,297-307 (2000)]. As pointed out elsewhere in this memorandum, the recently-submitted studies do **not** demonstrate that the young animal is less sensitive to the effects of atrazine than the adult animal. The FQPA Safety Factor was **retained due to residual concerns** identified by the HIARC for the effects of the neurocrine mode of action described for atrazine on the development of the young. The concern results from a lack of an assessment of exposure of the young animal to atrazine **throughout development.** Additionally, the residual concerns for the young animal are not just for disruption of the ovulatory process and reproductive effects, but for possible effects on the function of numerous other metabolic processes, including bone formation, and immune, CNS, and cardiovascular functions. Further, the 10X FQPA safety factor determination for atrazine was not only based on uncertainties in the hazard data for the immature animal but on the limitations found in the exposure monitoring data for drinking water.

CONCLUSION: The two recently-submitted special studies on young female SD rats do not demonstrate that the young animal is less sensitive to the effects of atrazine than the adult animal. The endpoint used for risk assessment for all population subgroups [LH surge attenuation and estrous cycle alterations] serves as a surrogate for the effects of atrazine on the hypothalamus-

pituitary axis/function. It is considered appropriate for all populations and is being used for the intermediate-term and long-term risk assessments. Additionally, there are no studies in the young animal of sufficient duration for use in these latter two assessment. The FQPA Safety Factor was retained due to residual concerns for the effects of the neuroendocrine mode of action on the development of the young. The concern results from a lack of an assessment of exposure of the young animal to atrazine throughout development. Finally, the 10X FQPA safety factor determination for atrazine was not only based on uncertainties in the hazard database for the immature animal but on the limitations found in the exposure monitoring data for drinking water.