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MEMORANDUM

SUBJECT: Review of Atrazine Cancer Epidemiology
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This review summarizes scientific studies related to atrazine and cancer epidemiology including a consideration of animal mode of action related to selected cancers. The review starts with an examination of animal mode of action issues related to prostate and ovarian cancers and non-Hodgkin's lymphoma. This section is followed by a review of EPA findings concerning prostate cancer in a manufacturing plant, the Agricultural Health Study, and two California studies. The following section addresses the evidence concerning non-Hodgkin's lymphoma and then, other cancers. The review concludes with a summary of three published reviews of atrazine and cancer epidemiology published 1996-1999, followed by a listing of those studies published since 1999 and considering their impact on the weight-of-evidence. In order to be comprehensive all known epidemiologic studies of atrazine and triazines have been included.

The U.S. Environmental Protection Agency (EPA) requested a review of atrazine and

prostate cancer by the Scientific Advisory Panel (SAP) made up of outside experts. A report of the
SAP findings (meeting minutes) from the July 17, 2003 meeting can be found at http://www.epa.gov/scipoly/sap/. This review considers the SAP findings and, where appropriate, revises the Agency's findings related to atrazine and prostate cancer. This review also explains why studies of other cancers where not presented to the Panel at the July 2003 meeting. To assist the reader, an outline of this review is provided below:

I. Examination of prostate and ovarian cancers and NHL in the context of the animal mode of action
II. Atrazine and prostate cancer epidemiology
    A. Prostate Cancer - Manufacturing plant study
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    C. Prostate Cancer - Pesticide use data and cancer incidence in California counties
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III. Atrazine and epidemiology of Non-Hodgkin's Lymphoma
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VI. Studies published since 1999 or not included in the three published reviews
VII. EPA Conclusion: Atrazine exposure and NHL and other cancers

I. Examination of prostate and ovarian cancers and NHL in the context of the animal mode of action

As discussed in the January 31, 2003 Interim Reregistration Eligibility Decision, atrazine's mode of action (i.e., a decrease LH surge, failed ovulation and estrous cycle disruption) for induction of mammary gland tumors (the only tumor observed in animal bioassays) in SD female rats is not considered relevant to humans. Because the epidemiology literature on atrazine (triazines) report that atrazine exposure may be associated with an increased incidence of prostate and ovarian cancers and NHL, the available chronic toxicity animal bioassays were closely examined for any indication of either prostate, ovarian cancer or NHL, as well as the etiology of these tumor types.

The prostate glands in male laboratory animals do not appear to be a target of atrazine toxicity. Subchronic and chronic rodent and dog studies and the multigeneration rat studies conducted for atrazine and its major metabolites have not demonstrated treatment related tumors or prostatitis and only shown inconsistent changes in prostates weights. The SD and Fisher rats and CD-1 mice are poor models for evaluating prostate cancer. Atrazine has been shown to result in prostatic inflammation of the adult rat offspring (Stoker et al., 1999) but this is not due to direct treatment of the offspring, but rather treatment of the dams. In this case, atrazine leads to a decrease in early lactational exposure to prolactin (via treatment of the mothers). Alterations in neonatal prolactin regulation lead to hyperprolactemia, which in turns lead to the prostatic inflammation found in the adult offspring. This work supports the neuroendocrine mode of action

for atrazine rather than a mode of action that would explain prostate cancer in adult male workers. Although the etiology of prostate cancer is not clearly understood, the hormonal changes caused by atrazine would be in the opposite direction (i.e., decreased prolactin) of what would be expected for the development of prostate cancer. Furthermore, it has not been clearly established that prostatitis increases the risk to prostate cancer. Therefore, the animal data do not support a mechanism for atrazine contributing to the onset or promotion of prostate cancer in humans.

Ovarian tumors in most laboratory animals are a rare occurrence (Damjanov, 1989). A dose-related increase in ovarian tumor incidence is not seen in any study using atrazine, simazine or propazine, and in all studies, the incidences of ovarian tumors are (as would be expected) very low. Although the causes of ovarian cancer are not definitively known, the key events in the mode of action established for atrazine, i.e., decreased serum LH levels and a decreased number of ovulations over a lifetime, are the opposite of the events hypothesized to be associated with ovarian carcinogenesis. Some hypotheses have been advanced for ovarian carcinogenesis with the predominant hypotheses being the "incessant ovulation" hypothesis and the "gonadotropin" hypothesis (e.g., Fathalla, 1971). This hypothesis suggests that damage to the ovarian epithelium, resulting from frequent ovulations, leads to increased risk of cancer as this leads to increased epithelial cell proliferation. It should be noted that epidemiology studies show that factors which decrease the number of lifetime ovulations - such as pregnancy, breast-feeding and oral contraceptive use - reduce ovarian cancer risk (Berchuck and Carney, 1997). Therefore, animal data do not support a biologically plausible mechanism for atrazine contributing to ovarian cancer in humans.

There was not an increase in any dose group for a lymphoma of any type, including non-Hodgkin's lymphomas (NHL) in atrazine treated SD or F344 rats. The simazine chronic bioassay using both sexes of SD rat also failed to see any lymphomas in any animal in any dose group (McCormick, 1988). Likewise, no animal in either of the two groups examined (control and high dose tested - 1000 ppm) in the propazine chronic bioassay, had a lymphoma of any type (Jessup, 1980). The alterations in reproductive hormones that atrazine exposure is associated with have not been linked to an increased risk of NHL. NHLs are a broad group of neoplasias which originate from lymphoid tissues such as B-cells, T-cells and histiocytes, though the vast majority are B-cell in origin. The etiology of NHLs are unclear. Generally speaking, increased risk of developing NHL appears to be associated with conditions or xenobiotic exposures that result in immune dysfunction (Scherr and Mueller, 1996). An association between NHL and reproductive hormones such as LH, FSH, estrogens and prolactin, does not appear to be present. A mechanistic role for atrazine contributing to NHL has not been identified in laboratory studies.

In summary, multiple animal bioassays do not reveal an increased incidence of tumors at any endocrine site other than mammary gland in female SD rats. Other endocrine tumors that have been raised in epidemiological studies can not be biologically tied to atrazine's mode of action (i.e., decrease prolactin, decrease LH and suppression of ovulation). Thus, at this time, based on the available animal cancer and mode of action data and epidemiological studies, there is no tumor endpoint on which to base a cancer risk assessment for atrazine. EPA has considered

other possible modes of action (e.g., stimulation of aromatase activity) and finds that there are inadequate data to support these hypotheses. EPA's Office of Research and Development National Health and Environmental Effects Laboratory is currently conducting a detailed investigation of the effects of atrazine and related chlorotriazines on aromatase activity and steroidogenesis in an effort to determine whether or not these compounds can change estrone, estradiol and testostosterone synthesis in response to atrazine treatment in rats. As additional data become available, EPA will review them.

Berchuck A, Carney M. Human ovarian cancer of the surface epithelium. Biochem Pharmacol. 1997 Sep 1;54(5):541_4.

Bosland MC. Male reproductive system. In Carcinogenesis. Eds., MP Waalkes, JM Ward. New Your: Raven Press, Ltd., 1994, pp. 339-402.

Damjanov I., Ovarian tumours in laboratory and domestic animals. Curr Top Pathol. 1989;78:1_10.

Fathalla MF. Incessant ovulation__a factor in ovarian neoplasia? Lancet. 1971 Jul 17;2(7716):163.

Jessup, D. 1980. Two year oral chronic toxicity study in rats. IRDC study no. 382-007. MRID 00041408; Acc. No. 219502401.

McCormick, C.C. and Arthur, A.T. Simazine-Technical: 104-Week Oral Chronic Toxicity and Carcinogenicity Study in Rats. 1988. Study Number: 2-0011-09. MRID number: 406144-05. Pharmaceuticals Division, Ciba-Geigy Corp., Summit, NJ.

Scherr PA and Mueller NE, Non-Hodgkin's lymphomas, in Eds D. Schottenfeld and JF Fraumeni Jr.. Cancer Epidemiology and Prevention New York, Oxford University Press, 1996, pgs. 920-945.

Stoker, T.E., Robbinette, C.L., Cooper, R.L. 2000.Maternal exposure to atrazine during lactation suppresses suckling_induced prolactin release and results in prostatitis in the adult offspring. Toxicol Sci. 1999 Nov;52(1):68_79.

II. Atrazine and prostate cancer epidemiology

The following review addresses epidemiology related to prostate cancer, non-Hodgkin's

lymphoma, other cancers and includes a brief summary of earlier reviews and the most recently submitted studies related to atrazine and triazines.

A. Prostate Cancer - Manufacturing plant study

An epidemiology study was conducted of workers at the Syngenta St. Gabriel plant where atrazine is manufactured. That study reported a statistically significant increase in the incidence of prostate cancer among plant workers. The Agency, upon review of this study, requested additional information on the exposure profile of the employees diagnosed with prostate cancer and this information was provided and reviewed. To further analyze the question of exposure a nested case-control study was proposed by Syngenta and conducted for them by Health Practice Exponent Inc. (Hessel et al. 2003). Preliminary results of this study, a review by the Agency, comments from four external peer reviewers, a Syngenta-sponsored expert panel review, and comments by the Natural Resources Defense Council were provided to the EPA's Scientific Advisory Panel in July of 2003. EPA's view of the study was that the increase in prostate cancer observed in the St. Gabriel workers was probably due to the increase in PSA screening for these workers.

The Panel was requested to comment on the Agency's conclusion regarding prostate cancer and particularly the results from this study. The specific Agency conclusion that EPA asked the SAP to comment on was: "Due to the lack of a detailed exposure analysis based on job history and the limited statistical power due to the small sample size, atrazine could not be ruled out as a potential cause but a role for atrazine seems unlikely."

The Panel's analysis of the St. Gabriel study differed to a degree from the Agency's conclusion. The SAP did conclude that "the increase in Prostate Specific Antigen (PSA) screening at the St. Gabriel plant likely led to an increase in the detection of cases of prostate cancer." Further, the Panel noted that "[s]ubstantive and persuasive arguments have been made to support the EPA's conclusion that PSA screening could explain the observed increase in prostate cancer incidence in the workers." Nonetheless, the Panel did not believe there was sufficient evidence to conclude that it was "unlikely" that atrazine had a role in the increased prostate cancer cases "given the severe limitations of the St. Gabriel study, particularly those pertaining to small sample size, questionable exposure assessment and lack of an appropriate comparison group." According to the SAP, PSA screening may be only a "partial explanation" for the increase in prostate cancer and that "atrazine cannot be ruled out as a potential cause."

The Agency agrees with the SAP's analysis and has rewritten its conclusion as follows:

The increase in prostate cancer incidence at the St. Gabriel plant in Louisiana is consistent

> with the intensive PSA screening. This is because prostate cancer was found primarily in active employees who received intensive prostate specific antigen (PSA) screening, there was no increase in advanced tumors or mortality, and proximity to atrazine manufacturing did not appear to be correlated with risk. No evidence was identified that permit a determination that some of the increase was likely due to exposure to atrazine although atrazine exposure cannot be ruled out at this time. However, the study was insufficiently large and suffered from other limitations that prevent a determination that all of the increase in prostate cancer was probably due to the intensive screening program.

One of EPA's external reviewers agreed with this finding regarding the role of PSA screening. Dr. Edward Giovannucci of the Harvard School of Public Health stated, "Thus, the increased excess of prostate cancer observed in the Novartis study is compatible with increases expected in a population that is receiving intensive PSA screening." Another reviewer, Dr. Aaron Blair of the National Cancer Institute, though not in full agreement with Dr. Giovannucci, agreed that there was evidence to "suggest that PSA screening may well explain the excess incidence of prostate cancer in this cohort."

The Scientific Advisory Panel suggested that the Agency consider additional analysis of the St. Gabriel cohort. However, the resulting sample size would still limit the opportunity to draw further conclusions. The Agency questions whether additional analysis is warranted for other potential risk factors (such as smoking, diet and previous work history, and non-occupational or pre-employment exposure to triazine herbicides). Because of the way the study was designed this information is not available to investigators and it may not be feasible to obtain such information. The same applies to the suggested analysis of family history, history of prostate disease, (e.g., benign prostatic hypertrophy and prostatitis), and additional biologic samples that allow DNA extraction. The St. Gabriel study was a study based on available records and it might be difficult or impossible for investigators to obtain permission from all or most subjects or next-of-kin to get the additional information outlined by the SAP. The SAP repeatedly acknowledges "The St. Gabriel cohort study suffered from several limitations that could lead to negative findings in epidemiologic studies of similar design, particularly with regard to the very small sample size" which can greatly hinder the statistical power to detect an effect.

In October, 2003, Syngenta provided a completed report on the nested case-control study (cases and controls selected from within the cohort) by Health Practice Exponent Inc. that examined in more detail the exposure of 12 of 17 prostate cancer cases and examined the effect of screening on prostate cancer incidence (Hessel et al. 2003). EPA has not yet reviewed this study in depth, but a preliminary reading did not find any evidence that prostate cancers could be attributed to atrazine exposure. Statistical analysis suggest that PSA screening would explain some or all of the elevated rates of prostate cancer. The study authors concluded "There is no evidence for an association between atrazine exposure and prostate cancer among the workers at the Syngenta plant in St. Gabriel. The increased incidence of prostate cancer observed in the previous study could be explained by the PSA screening program."

B. Prostate Cancer - Agricultural Health Study in Iowa and North Carolina

Tied into the assessment of atrazine and prostate cancer is the recently published study Alavanja et al. (2003). This large prospective cohort study of 55,332 male pesticide applicators, known as the Agricultural Health Study, reported on the risk of prostate cancer and computed odds ratios for individual pesticides within the cohort. For atrazine the reported odds ratio (ratio of odds in favor of disease among exposed to the odds of disease among the unexposed, an odds ratio of 1.0 implies no increased risk from exposure) was 0.94 for ever/never use reported by questionnaire with a 95% confidence interval of 0.78 to 1.14. The Agricultural Health Study has a number of advantages over other epidemiologic studies of pesticides. It is the largest study of its kind, determines exposure prior to disease (thus, eliminating recall bias), analyzes a wide variety of potential and known confounders including other pesticide exposures, and has greater statistical power to detect small effects.

The Scientific Advisory Panel expressed concern that the use of ever/never use atrazine was "likely an inappropriate exposure metric" and that other factors such as measures of continuous or intermittent use should be considered. The Panel appeared to place little weight on the dose-response analysis based on cumulative exposure which combined duration, frequency, and intensity into one metric that did not show any association between atrazine and prostate cancer. The Agency agrees that other exposure metrics might be considered but disagrees that ever/never use and cumulative exposure is an inappropriate measure. Available pesticide usage data suggest that the pattern of use of atrazine as a preharvest herbicide limits variability in duration, frequency, and intensity of use and the dose-response analysis is a sufficient measure to account for this source of variation.

The Scientific Advisory Panel expressed concern that this study had a short follow-up period "with exposure information collected at the start of follow-up" and incorrectly stated this was less than five years. Because study subjects were queried about past as well as present use of atrazine, the follow-up period was much longer than five years. The National Cancer Institute is planning to redo the prostate cancer study with a much larger cohort next year when the sample size will be approximately twice as large. However, given the relatively tight confidence interval on the current estimate and the lack of any evidence of dose-response, the Agency does not expect the new study to produce results different from those already reported. Nevertheless, the Agency will revisit and revise these conclusions if the updated prostate cancer study produces different results suggesting a risk from exposure to atrazine.

C. Prostate Cancer - Pesticide use data and cancer incidence in California counties

Two studies were conducted in California which has maintained a population-based cancer registry since 1988 and a state-wide pesticide use reporting system. Mills (1998) obtained 1993

pesticide usage data for six pesticides with a suspicion of carcinogenicity based on other toxicologic and epidemiologic studies. These data were compared using regression analysis with county age- and race- adjusted cancer incidence rates (1988-92). A borderline statistically significant correlation was found between atrazine usage and prostate cancer in black males, but not among Hispanic, White, or Asian males. This study is subject to aggregation bias because the exposure of individuals in the county was not measured. EPA considers such studies useful for guiding future studies, but not for reaching conclusions about causation.

A second study by Mills and Yang (2003) examined the effect of simazine rather than atrazine on prostate cancer among members of the United Farm Workers of America. The study found a borderline significant association between high simazine use and prostate cancer. Like the earlier Mills (1998) study, this study suffers from aggregation bias and a crude measure of exposure (total poundage of active ingredient by crop and county for a given time period) which may not reflect exposure among farmworkers, 90% of whom are not actively involved in applying or handling pesticides (1999-2002 data from presentation on National Agricultural Workers Survey by S. Gabbard, J. Nakamoto, and D. Carroll, September 24, 2003, funded by the Department of Labor). The use of total poundage of active ingredient by county was not normalized by number of workers and is especially problematic because it correlates with the size of the crop and acreage in the county and many other factors which might have little to do with exposure of farmworkers. For example, a county with double the poundage would be counted as having double exposure, even if it also had double the number of farmworkers and their exposure was the same in both counties.

D. Prostate Cancer - Overall conclusion

Studies of manufacturing and farming populations do not support a finding that atrazine is a likely cause of prostate cancer. The Scientific Advisory Panel stated that neither the Syngenta St. Gabriel Plant study or the Agricultural Health Study were "sufficient for EPA to conclude that there is no causal association between atrazine exposure and prostate cancer." However, the Agency does not find any results among these studies that would lead us to conclude that potential cancer risk is likely from exposure to atrazine.

III. Atrazine and epidemiology of non-Hodgkin's lymphoma

The National Cancer Institute has performed a number of studies of non-Hodgkin's lymphoma (NHL) in farming populations. The key findings related to atrazine are noted below.

A study by Schroeder et al. 2001 examined two subtypes of NHL for association with pesticide exposure based on earlier data from Iowa and Minnesota. The negative NHL subtype was significantly associated with 5 pesticides. For atrazine, the odds ratio was borderline significant (Odds ratio = 1.7 with 95% confidence interval 1.0-2.8). The Schroeder study

cautiously stated "In conclusion, we found weak to relatively strong associations between many agricultural exposures and t(14;18)-positive, but not t(14;18)-negative NHL." and "Causal relationships . . . are plausible, but associations should be confirmed in a larger study."

The study by Schroeder et al. (2001) contrasted with an earlier study by Zahm et al. (1993) conducted in these same two states plus Kansas and Nebraska which concluded, "In our judgment, these data provide little evidence that atrazine is associated with NHL among white men."

Added to these two conflicting studies is a study by DeRoos et al. (2003) published electronically in September 2003. EPA has not had time to review this study in depth, but did not find evidence sufficient to implicate atrazine as a likely cause of NHL. This study stated that "Reported use of several individual pesticides was associated with increased NHL incidence" but that "limitations of our data hinder the inferences we can make regarding specific pesticides". The hierarchical regression odds ratio (odds ratio adjusted for the effect of exposure to other pesticides) for atrazine was 1.5 (95% CI = 1.0 to 2.2) which, like the study by Schroeder et al (2001), has borderline significance. Studies with borderline significance increase the likelihood that chance or some confounder may be an explanation for the observed findings. The authors caution that "some of the positive results could be due to chance" though adjustment for the influence of other pesticides in the analysis makes this somewhat less likely.

Given the conflicting results and the extreme caution exhibited by the National Cancer Institute (NCI) in making its conclusion regarding specific pesticides, the EPA has concluded that evidence is not sufficient to implicate atrazine as a likely cause of non-Hodgkin's lymphoma. Nevertheless, EPA will consider these studies in conjunction with other evidence and may request additional external review. An exhaustive and thorough analysis of non-Hodgkin's lymphoma and pesticide use is planned by NCI for 2004-5. This analysis will include consideration of NHL subtypes and many other factors as well. Absent compelling information in the interim, EPA has determined that a thorough review of atrazine and NHL should be conducted when the NCI data are available.

IV. Atrazine and epidemiology related to other cancers

Other cancers besides prostate and non-Hodgkin's lymphoma were found to have an elevated, though not statistically significant, increase in risk at the St. Gabriel plant (Delzell et al. 2001). Other studies have suggested an increased risk for ovarian, breast, and other cancers. However, these studies are at best preliminary and should not serve as a basis for implicating atrazine as a human carcinogen due to their methodological limitations and the absence of replication in other populations. The National Cancer Institute is planning a review of atrazine and all types of cancers in 2004. Given the much larger sample size and strengths of this Agricultural Health Study, the Agency has decided further review of other cancers and atrazine should take place when results from this planned analysis are available. However, if other studies

or additional compelling evidence becomes available in the interim, the Agency will expeditiously review the new evidence and the potential risk resulting from exposure to atrazine. A summary of evidence from previous reviews of atrazine and cancer epidemiology, and studies published subsequently, are reviewed in the following section

V. Results of other reviews of cancer and atrazine through 1999

Three reviews of triazines including atrazine and cancer epidemiology have been reported in the 1996-1999 time period:

IARC. 1999. IARC Monographs on the evaluation of carcinogenic risks to humans. Volume 73: Some chemicals that cause tumours of the kidney or urinary bladder in rodents and some other substances. World Health Organization, Lyon, France.

Neuberger JS. 1996. Atrazine and/or triazine herbicides exposure and cancer: an epidemiologic review. *Journal of Agromedicine* 3(2):9-30.

Sathiakumar N, Delzell E. 1997. A review of epidemiologic studies of triazine herbicides and cancer. *Critical Reviews in Toxicology* 27:599-613.

These three reviews identified the 10 case-control studies (see numbered references at the end of this review, 1-10) and two published cohort studies of workers exposed to triazines at manufacturing plants (11-12).

Neuberger (1996) concluded "based on the data to date . . . there is no convincing evidence of a causal association between atrazine and/or triazine(s) and colon cancer, soft tissue sarcoma, Hodgkin's disease, multiple myeloma, or leukemia. . . .There is a suggestion of a possible association between atrazine and/or triazine(s) with ovarian cancer and non-Hodgkin's lymphoma. However, the ovarian cancer study needs to be replicated and the NHL studies fall short of providing conclusive evidence of risk because the results could be due to chance, bias, or confounding."

Sathiakumar and Delzell (1997) concluded "The available epidemiologic studies, singly and collectively, do not provide any consistent, convincing evidence of a causal relationship between exposure to triazine herbicides and cancer in humans."

The International Agency for Research on Cancer (1999) summarized the human carcinogenicity data as follows:

> A combined analysis of results of two cohort studies of agricultural chemical

production workers in the United States showed decreased mortality from cancers at all sites combined among the subset of workers who had had definite or probable exposures to triazine. Site-specific analyses in this subset of workers yielded no significant findings; a non-significant increase in the number of deaths from non-Hodgkin's lymphoma was seen, but was based on very few observed cases.

A pooled analysis of the results of three population-based case-control studies of men in Kansas, eastern Nebraska and Iowa-Minnesota, United States, in which the risk for non-Hodgkin's lymphoma in relation to exposure to atrazine and other herbicides on farms was evaluated, showed a significant association; however, the association was weaker when adjustment was made for reported use of phenoxyacetic acid herbicides or organophosphate insecticides. A sub-analysis of results for farmers in Nebraska, the State in which the most detailed information on atrazine use was available, showed no excess risk for non-Hodgkin's lymphoma among farmers who had used atrazine for at least 15 years, after adjustment for use of other pesticides. In a case-control study of non-Hodgkin's lymphoma among women in eastern Nebraska, a slight, nonsignificant increase in risk was seen. In all these studies, the farmers tended to have an increased risk for non-Hodgkin's lymphoma, but the excess could not be attributed to atrazine.

Less information was available to evaluate the assoication between exposure to atrazine and other cancers of the lymphatic and haematopoietic tissues. One study of Hodgkin disease in Kansas, one study of leukaemia in Iowa-Minnesota and one study of multiple myeloma from Iowa gave no indication of excess risk among persons handling triazine herbicides.

In a population-based study in Italy, definite exposure to triazines was associated with a two- to threefold increase of borderline significance in the risk for ovarian cancer. The study was small, and potential confounding by exposure to other herbicides was not controlled in the analysis.

Based on these findings the IARC concluded "There is inadequate evidence in humans for the carcinogenicity of atrazine." In a critique of IARC monographs, Huff (2002) questioned the decision on atrazine and animal carcinogenicity and based this partly on the Delzell et al. (2001) report showing increased risk for prostate cancer and above expected levels for certain cancers including buccal cavity (3 observed, 2.1 expected), esophagus (2 observed, 0.7 expected), stomach (2 observed, 0.9 expected), bladder (3 observed, 1.6 expected), thyroid (2 observed, 0.6 expected) and leukemia/lymphomas (7 observed, 4.5 expected). These data are based on Table 7 of the Syngenta report by Delzell et al. (2001). This table shows 9 different estimates of risk, not counting prostate (already discussed) and certain grouped categories. Therefore, 6 of 9 categories exhibited an excess, though statistically insignificant risk. Chance alone is a possible explanation for such findings. In addition, bias and confounding could produce such results. Therefore, these elevated, nonsignficant incidence ratios must be considered preliminary findings. Until these findings are replicated in other studies that address the serious methodological

limitations (especially the low statistical power) of the present study, they should be regarded as spurious or suggestive at best. Therefore, the EPA disagrees with Huff (2002) that the epidemiology studies provide support for a revision of the IARC classification for atrazine.

Independent of these three reviews, EPA has performed internal reviews of all of the above studies which had statistically significant findings relevant to atrazine or triazines including additional updates to the manufacturing plant studies submitted to EPA but not published. With the exception of the possible association with ovarian cancer, which EPA reviewers stated needed to be confirmed in other populations, the Agency did not find convincing evidence of an association between triazines or atrazine and cancer.

Huff J. 2002. IARC monographs, industry influence, and upgrading, downgrading, and under_grading chemicals: a personal point of view. International Agency for Research on Cancer. *Int J Occup Environ Health*. 8(3):249-70.

VI. Studies published since 1999 or not included in the three published reviews

The following six studies were reviewed by EPA and submitted to the Scientific Advisory Panel for review in July 2003.

Alavanja MCR, Samanic C, Dosemeci M, et al. 2003. Use of agricultural pesticides and prostate cancer risk in the Agricultural Health Study cohort. *Am J Epidemiol* 157:800-814.

Delzell E, et al. 2001. Cancer Incidence Among Workers in Triazine-related Operations at the Novartis St. Gabriel Plant" Oct. 12, 2001. MRID# 451521-01 and 455184-01, Chemical #080803. [Technical Report 170 pp.]

MacLennan PA, Delzell E, Sathiakumar N, et al. 2002. Cancer incidence among triazine herbicide manufacturing workers. *J Occup Environ Med.* 44:1048-1058.

MacLennan PA, Delzell E, Sathiakumar N, et al. 2003. Mortality among triazine herbicide manufacturing workers. *J Toxicol Environ Health A* 66(6):501-517.

Mills PK. 1998. Correlation analysis of pesticide use data and cancer incidence rates in California counties. *Arch Environ Health*. 53:410-3.

Mills PK, Yang R. Prostate cancer risk in California farm workers. 2003. *J Occup Environ Med*. 45:249-258.

Results from the Alavanja (2003), Delzell (2001), Mills (1998), and Mills and Yang (2003) have already been discussed above. The two reports by MacLennan et al. are updates to the two earlier reports by Sathiakumar (1992, 1995). Most of the results in these two studies are covered in much more detail by Delzell et al. (2001) which has already been discussed above in

the sections on prostate cancer and other cancers. The mortality study (MacLennan et al. 2003) did find a borderline significant result for non-Hodgkin's lymphoma based on 4 observed deaths versus 1.1 deaths expected. The authors noted, however, that "one of the decedents whose death certificate included a diagnosis of NHL had medical records, including a biopsy report that indicated a diagnosis of poorly differentiated nasopharyngeal cancer. This case was not removed from our analysis. To have done so would have introduced a bias because there is no satisfactory procedure for removing similarly misclassified cases from the numerator of general population mortality rates used to calculate the expected number of deaths. Our data were not of adequate statistical precision to demonstrate trends in NHL rates or SMRs by years worked and years since hire." This acknowledgment of bias based on a misclassified case means that borderline statistically significant finding would no longer be significant if the case were excluded. As stated above, this evidence is not sufficient to support a finding that atrazine is a likely cause of non-Hodgkin's lymphoma.

The following six studies, including two published since July 2003 meeting were not submitted to the Scientific Advisory Panel.

De Roos AJ, Zahm SH, Cantor KP, Weisenburger DD, Holmes FF, Burmeister LF, Blair A. 2003. Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men. *Occup Environ Med* 60:e11.(http://www.occenvmed.com/cgi/content/full/60/9/e11)

Hessel PA, Kalmes R, Smith TJ, Lau E, Mink P, Mandel J. 2003. A Nested Case-Control Study of Prostate Cancer and Atrazine Exposure. Final Report, October 3, 2003 performed by Health Practice Exponent, Inc. and submitted by Syngenta Crop Protection, Inc.

Hopenhayn-Rich C, Stump ML, Browning SR. 2002. Regional assessment of atrazine exposure and incidence of breast and ovarian cancers in Kentucky. *Arch Environ Contam Toxicol* 42:127-136.

Kettles MA, Browning SR, Prince TS, Horstman SW. 1997. Triazine herbicide exposure and breast cancer incidence: an ecologic study of Kentucky counties. *Environmental Health Perspectives* 105:1222-1227.

Schroeder JC, Olshan AF, Baric R, et al. 2001. Agricultural risk factors for t(14;18) subtypes of non-Hodgkin's lymphoma. *Epidemiology* 12:701-709.

Van Leeuwen JA, Waltner-Toews D, Abernathy T, et al. 1999. Associations between stomach cancer incidence and drinking water contamination with atrazine and nitrate in Ontario (Canada) agroecosystems, 1987-1991. *Int J Epidemiol.* 28:836-40.

DeRoos et al. (2003), Hessel et al. (2003), Schroeder et al. (2001) have already been discussed above. Hessel et al. (2003) is discussed at the end of the section on "Prostate Cancer - Manufacturing Plant Study". DeRoos et al. (2003) and Schroeder et al. (2001) are discussed in

the section on non-Hodgkin's lymphoma.

The other three studies by Hopenhayn-Rich et al. (2002), Kettles et al. (1997), and Van Leeuwen et al. (1999) are ecological studies where the unit of analysis are populations or groups of people rather than individuals. An earlier study by Kettles et al (1997) suggested an association between triazine exposure and breast cancer in Kentucky. However, a later follow-up study by Hopenhayn-Rich et al. (2002) did not support this finding for Kentucky and instead found results suggesting a protective effect for atrazine for ovarian cancer and no effect on breast cancer. The Hopenhayn-Rich et al. study was based on 5 year, age-adjusted cancer rates which are likely to be more stable than the two year rates used by Kettles et al. A study by Van Leeuwen et al. (1999) found a positive association between atrazine water contamination levels and stomach cancer among 40 ecodistricts in Ontario, Canada, and a negative association with colon cancer suggesting a protective effect for atrazine. The authors "noted that so-called 'ecologic studies', the type of analysis conducted in this research, have a number of weaknesses, including ecologic fallacy and multiple collinearity." Stomach cancer has been declining for many years and is likely associated with a number of dietary and lifestyle factors, not controlled for in the Van Leewen et al. (1999) study (Cancer Rates and Risks, 4th edition, National Cancer Institute 1996). All of these studies are subject to aggregation bias because the actual exposures of individuals in the county/district or how long they resided there is not known. As noted in standard epidemiology texts, ecologic studies "can suggest avenues of research that may be promising . . . In and of themselves, however, they do not demonstrate that a causal association exists" (Gordis L. Epidemiology. W.B. Saunders Company, Philadelphia, 1996). The authors themselves warn "conclusions concerning causality cannot be drawn" (Kettles et al. 1997). An ecologic study in Kentucky of similar design to those above, found a whole host of factors that vary across an urban-rural gradient (Blondell JM. Urban-rural factors affecting cancer mortality in Kentucky, 1950-1969. Cancer Detection and Prevention 11:209-223, 1988). Persons living in rural areas differ not only in terms of pesticide exposures, but also diet, parity, physical activity, exposure to viruses, and other lifestyle factors. Appropriate controls are critical when studying the relationship between pesticide exposure and cancer.

VII. EPA Conclusion: Atrazine exposure and NHL and other cancers

The Agency does not find any results among the available studies that would lead us to conclude that potential cancer risk is likely from exposure to atrazine. EPA plans to revisit this conclusion upon receipt of new studies, especially those from NCI's Agricultural Health Study on atrazine and all cancers, prostate cancer, and non-Hodgkin's lymphoma, all of which are planned for completion in the next 1-2 years.

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cc: atrazine file (080803)
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