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

OFFICE OF PESTICIDES AND PREVENTION, TOXIC SUBSTANCES

January 15, 2003

MEMORANDUM

SUBJECT: Review of Additional Data on Potential Atrazine Exposure and Review Comments Submitted by Syngenta and NRDC on Atrazine Cancer Epidemiology Study: "Follow-up Study of Cancer Incidence Among Workers in Triazine-related Operations at the Novartis St. Gabriel Plant" by Elizabeth Delzell et al.
DP Barcode D287278, MRID# 455184-01, Chemical #080803

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BACKGROUND

This review considers additional information submitted by Syngenta Crop Protection, Inc. and public comment on the exposure of workers with cancer diagnosed at the St. Gabriel Plant in Louisiana. An earlier review (D281568, March 25, 2002) considered the results of a cancer incidence study at this plant. Additional exposure information has been provided in a report transmitted to the Office of Pesticide Programs (OPP) on November 1, 2002 titled "Summary of Information on Potential Atrazine Exposure for 12 out of 17 Prostate Cancer Cases Reported by Delzell et al. 2001" by Charles B. Breckenridge. In addition to this report, OPP also received comments from the Natural Resources Defense Council (NRDC, June 3 and July 30, 2002) and a panel report titled "An Evaluation of the Report by Dr. Delzell et al. on "'A Follow-up Study of Cancer Incidence Among Workers in Triazine-Related Operations at the Novartis St. Gabriel plant'" submitted by Hans-Olov Adami, Graham Colditz, Jack Mandel,

and Dimitrios Trichopoulos.

The primary purpose of this review is to consider the newly submitted exposure information, the NRDC comments, and the panel report. The following background information is quoted from the March 25, 2002 review (Blondell 2002, DP Barcode D281568):

Periodically, Novartis has reported to EPA on an ongoing epidemiologic study of workers at the St. Gabriel plant in Louisiana. The main product of this plant during most of its history was triazine herbicides. See the “Review of Two Atrazine Epidemiology Studies” by Jerome Blondell (D226645, MRID #s 440086-01, 440086-02) which summarizes the earlier studies. See also the “Review of five atrazine epidemiology published articles for SAP” by Ruth Allen (D262405) for a review of the most recently published studies concerning atrazine. The earlier review by Blondell (September 13, 1996) had the following conclusion:

> OREB [Occupational and Residential Exposure Branch] concludes that neither of the epidemiologic studies reviewed here adds significant new information concerning adverse health effects of atrazine. A non-significant elevation in non-Hodgkin's lymphoma continues to be observed at the Louisiana plant among workers exposed to triazines, including atrazine. By itself this study does not support a conclusion of increased cancer from exposure to triazines. However, this study could be considered supportive, but only supportive and not definitive, if evidence of an association between non-Hodgkin's lymphoma and triazine exposure was available from other studies. Follow-up by the National Cancer Institute in four states looked specifically to determine whether earlier associations in individuals studies could be attributed to atrazine when adjustment was made for exposures to other pesticides. They concluded that "detailed analyses suggested that there was little or no increase in the risk of NHL attributable to the agricultural use of atrazine.” The Occupational and Residential Exposure Branch concurs with this finding.

The more recent studies submitted by Novartis did not find additional evidence of risk of NHL, but focus principally on a statistically significant increase in prostate cancer. The earlier review concluded:

> This study did find a significant association between prostate cancer and working at the St. Gabriel plant where triazine herbicides, especially atrazine, was the main product of the plant during most of its history. Statistically significant risks were restricted to the Novartis employees rather than contract employees. However, these same employees were the most likely to undergo extensive PSA screening which likely accounts for most, if not all, of the observed increase, rather than an effect of atrazine exposure.

A severe shortcoming of this study was the inability to assess relative exposures among the workers at the plant. It was reported that eight of the 14 Novartis workers with prostate cancer worked at jobs that would have no more than "sporadic" exposure to atrazine and, apparently, though it was not well documented, exposure to other chemicals (e.g., cyanuric chloride, hydrogen cyanide) that might influence prostate cancer incidence. It is difficult to make any firm conclusions about the potential for atrazine to be the primary association with prostate cancer if over half of the cases had questionable exposure. The Health Effects Division supports the study authors suggestion that historical exposure data is used in a nested case-control study. Detailed plant work histories for individual subjects could be developed using work area, job-exposure, and information from biomonitoring and dust sampling.

The additional information submitted by Syngenta Crop Protection, Inc. provide descriptive information about the exposure of the prostate cancer cases working at the St. Gabriel plant. This information is reviewed below, followed by a review of comments received from NRDC and the panel report prepared by a separate panel of epidemiologists to review Dr. Delzell's report.

REVIEW OF ADDITIONAL EXPOSURE INFORMATION FOR PROSTATE CANCER CASES

At EPA's request, Syngenta prepared an atrazine exposure profile of employees diagnosed with prostate cancer. There were 17 cases, including 14 Syngenta cases and 3 contract employees. Exposure information was obtained for 12 of the 14 Syngenta employees. There was no exposure information available for the three prostate cancer cases among contract workers. However, contract workers accounted for 62% of the person years examined and their period of exposure was a median of 2.6 years compared to 20 years for Syngenta employees. These contract employees did not generally receive PSA screening and their numbers were not significantly higher than the 1.8 cases expected, based on using Louisiana as the comparison population. Using the local industrial corridor as a comparison population, the comparison would be 3 observed prostate cancer cases and 2.7 expected. Therefore, the Health Effects Division (HED) concludes that the absence of exposure information for contract employees is not of particular concern because the observed number of cases is close to expectation and the duration of exposure to atrazine is relatively low.

Two of the 14 Syngenta cases did not have the necessary information to classify by exposure but were concluded to have low exposure based upon their job titles. The remaining 12 cases were classified in two ways. First, job titles were obtained from commencement of employment until September 2002 or when employment ended. Jobs were then classified by their "proximity to locations

in the plant where atrazine is manufactured, handled, or packaged." Of the 30 different jobs, 5 were classified as remote, 17 were classified as low, 4 were classified as mid, and 4 were classified as high physical proximity to atrazine production. For each prostate cancer case, the proportion of time in each category of exposure was assessed and then cumulated up until the time of prostate cancer diagnosis. For the second method, a relative atrazine proximity scale was developed. Based on atrazine airborne dust monitoring data, remote, low, mid- and high proximity areas were found to differ by an order of magnitude. Thus, each category could be assigned a relative exposure factor of 0.1, 1, 10, and 100. This value was multiplied by the duration at each type of location and cumulated to create an index of exposure. This index of exposure also adjusted for substantial reductions in exposure due to changes at the plant in 1984-85.

Results from the method of classifying jobs by proximity found that the 12 cancer cases spent 46% of their plant time in low proximity positions, 26% in medium proximity, and 28% in high proximity to atrazine production. The majority of the high proximity time was due to three of the cancer cases spending the majority of their working time in these positions.

This analysis was supported by the cumulative index of exposure method. Three cases had high proximity to atrazine production throughout their working at the plant with a cumulative index greater than 10,000. Four cases had a medium exposure with a cumulative index greater than 1,000 and less than 10,000. The remaining five cases had a low exposure index (less than 1,000). As noted above, the two unassessed cases were likely to be low proximity based on their job titles.

Further analysis did not find any relationship between age at diagnosis and proximity to atrazine. Had their been such a relationship, it would have supported the possibility that atrazine was a causative factor in the subsequent diagnosis. All 12 of the employees with prostate cancer participated in the prostate cancer screening program and at least 10 of them were initially detected due to the PSA screening. Of the total 14 Syngenta cases, 12 had early stage localized prostate cancer and 2 had regional cancer within the prostate. "No distant, advanced stage, metastasized cancer was detected in Syngenta employees." Together these results are consistent with the conclusion that the observed significant excess in prostate cancer at the Syngenta plant in Louisiana was more likely an artifact of the extensive PSA screening program than a result of exposure to atrazine.

Additional Exposure Information not available to external peer reviewers:

The information provided above did not provide comparative information on non-exposed workers. This is a key shortcoming because if only a very small proportion of all workers were involved in the high exposure work areas, it could mean that the incidence of prostate cancer was much higher in these areas. Therefore, the following request was sent to Syngenta at the end of December 2002.

> Can you let us know what proportion of the workforce at the St. Gabriel plant work in the different buildings? Figure 1 from your report shows 18 buildings and only 4 of these were classified as medium or high proximity for atrazine exposure. It would be helpful to know even a rough average number of workers that spent time in the buildings classified as high, medium or low. Just having number for the prostate cancer cases makes it difficult to make any comparison or conclusion.

In response, Syngenta supplied the following information on January 16, 2003:

> Table 1 in the attached file now provides estimates of the number of male Syngenta employees at St. Gabriel excluding contract manufacturers as you requested. We have performed chi square tests of the observed and expected incidences of prostate cancer case based on 12 or 14 cases found in the St. Gabriel work force up to the end of 1999 . . .
>
> The results of the chi square analysis presented in Table 2 indicate that a higher than expected incidence of prostate cancer cases was distributed to the moderate proximity subgroup. Table 3 shows that when the low and moderate proximity subgroups are combined, the observed and expected incidence of prostate cancer cases are comparable.
>
> These results support the interpretation that there is no association between proximity to atrazine manufacture and the occurrence of prostate cancer among Syngenta employees at St. Gabriel.

A copy of Table 1 is reproduced below:

Table 1. Estimated Number (%) of Male Employees at St. Gabriel at the End of Each Year
(Syngenta Male Employees Only)

Proximity to Atrazine Manufacturing	Year			
	1977	1986	1996	2002
Low	205 (72%)	275 (77%)	306 (79%)	291 (80%)
Moderate	20 (7%)	20 (6%)	20 (5%)	19 (5%)
High	60 (21%)	60 (17%)	63 (16%)	55 (15%)
Total Number	285	355	389	365

Based on this Table, an average of 77% of Syngenta employees had low proximity to atrazine manufacturing; an average of 6% had moderate proximity; and 17% had high proximity to atrazine manufacturing. Of the 14 prostate cancer cases, 50% were classified as low proximity to atrazine manufacturing, 28% were classified as moderate proximity, and 21% were classified as high proximity. It appears that there would be no strong evidence of dose-response, although a higher proportion of workers (50% versus 23%) were involved in jobs with moderate or high proximity to atrazine manufacturing. However, no strong conclusions should be drawn from this crude comparison. A proper comparison would require measuring the exposure of cases and non-cases in the same manner and taking into account confounders such as age and person-years of exposure. Syngenta acknowledges this shortcoming and is planning a case-control study within the cohort to address this issue.

REVIEW OF COMMENTS FROM THE NATURAL RESOURCES DEFENSE COUNCIL

The Natural Resources Defense Council (NRDC) sent EPA two sets of comments concerning the prostate cancer in workers exposed to atrazine. NRDC noted that “these cancers appeared commonly in younger workers (almost every cancer case was a man under age 55), and are most common in those workers who spent the most time at the facility.” However, as discussed above and in the earlier review (Blondell 2002), the PSA screening at the plant was offered to relatively young workers. According to Table 19 of the Delzell et al. report, among active Novartis workers 40 years of age and over, just 7-9% were 55 years or older from 1989 through 1999. Thus, there was a very small number of workers over age 55 who participated in the PSA screening. Table 9 of the report generally found higher or roughly equal incidence ratios among workers who worked less than 5 years compared to workers who worked 5 years or more after stratifying for years since hire. One would have expected higher ratios among those with 5 or more years employment at the plant, if dose of atrazine was a factor contributing to prostate cancer. There was some evidence of a consistent pattern between duration of

exposure since hire and higher prostate cancer incidence ratios, but this was not consistent across subgroups and, in any case, was likely correlated to opportunity for and number of PSA screening tests.

NRDC criticized the Syngenta study for the lack of exposure information based on specific job descriptions which was crucial to examining whether chemical exposure was associated with the reported illnesses. This comment was echoed by the HED and other reviewers.

NRDC noted concern that “more than 200 workers were excluded from the study” who left Louisiana before 1988 because they might be more likely to develop cancer due to longer time since exposure. However, the study depends on the Louisiana Tumor registry for both the source of cases and controls and in such studies, it is appropriate to limit subjects to those that could be captured by the Tumor registry.

NRDC was concerned that the study population was over 60 percent contract workers who had relatively short exposure times and “were therefore far less likely to be at risk from chronic exposures”. However, it should be acknowledged that the Syngenta study stratified the analysis and examined the standardized risk incidence ratios for just the workers employed at the plant with much longer exposures. Therefore, HED disagrees with the conclusion that “the company likely diluted the apparent frequency that exposed individuals develop cancer”. Further statements by NRDC concerning the ability “to extract relevant information” and to show cancers were concentrated among plant employees who worked longer [and, therefore, had much more access to PSA screening] do not support a finding that results were “diluted” by including low exposure employees. NRDC notes prostate cancer cases had a median length of employment of 20 years, but should also have noted that this association applies to age and opportunity for PSA screening, two primary confounders of concern.

NRDC states that “Even if the study is correct to suggest that improved screening may account for some increase in cancer incidence, the number of cancers at the St. Gabriel facility cannot be explained merely by rigorous testing.” The question of the effects of screening is an important one. Other studies (Mettlin 2000, Roberts et al. 1999) have noted a two- to three-fold increase in age-adjusted prostate cancer incidence, while mortality increased by 20-50%. Both incidence and mortality were reported to decline after 1992 in these studies. Howe et al. (2001) commented:

> Following large increases in prostate cancer incidence due to the introduction of PSA screening in the late 1980s, the incidence trend has been stable from 1995 through 1998, while death rates have continued to decline for both white males and black males. Much of the geographic variation in prostate cancer incidence reflects differences in PSA screening, with regions of high PSA screening penetration having higher incidence rates, often because of the discovery of clinically insignificant tumors.

How much of the national prostate cancer incidence increase is due to PSA screening is unclear. The study in a Minnesota county (Roberts et al. 1999) found a three-fold increase in incidence among men, over 50% of whom, in their sixties and seventies, received PSA screening, a proportion characterized as “extremely high”. The six-fold increase reported at the Syngenta plant where nearly 100% received screening is not inconsistent with a conclusion that screening rather than some environmental factor is a major cause, and perhaps, the only cause for the jump in the incidence rate.

However, NRDC points out and HED agrees that one should be cautious at attributing all of the observed excess to screening rather than exposure to atrazine without further investigation. The report on exposure, subsequently received from Syngenta, found more prostate cancers among those with low or moderate exposure. This would seem difficult to attribute to atrazine unless there were some threshold effect, such that the risk of cancer did not follow a dose-response relationship, or unless there were errors in the measurement of exposure. Possible errors would mean that those in the low or moderate category, characterized as having exposures that were “low or below detection limits”, actually did have high exposures that were missed. For example, there might have been an unforeseen release leading to short-period of high levels of atrazine in the breathing space of employees otherwise exposed to only very low levels. Another possibility might be a temporary transfer of atrazine on dust particles that were transferred to low exposure workers, their food or water. These possibilities are at best speculative and given the limitation of significant exposure to only 4 of 18 buildings, they appear unlikely.

NRDC notes that one subset of workers, actively working at diagnosis had a nine-fold increase (11 cases, 1.2 expected). However, subsets of data should be expected to exhibit greater variation. The 95 percent confidence interval on the nine-fold increase shows the odds ratio may be expected to fall anywhere between 4.6 and 16.4. A weight-of-evidence determination would require much more consistency among various subsets with higher exposed subgroups exhibiting higher estimated rates of risk. Earlier, NRDC had claimed that those leaving the state were “those most likely to develop work-related cancer”, but this would be inconsistent with active workers, with a relatively shorter time since exposure, having the highest risk.

NRDC notes that a number of other cancers exhibited excesses, 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. 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.

Finally, NRDC charged that EPA disregarded other “epidemiologic studies linking atrazine to ovarian, prostate, testicular, and breast cancer, and to non-Hodgkin’s lymphoma.” Although it is true that the later EPA reviews had not addressed these specific studies in detail, earlier reviews examined the more important studies. The question of non-Hodgkin’s lymphoma (NHL) was addressed in the October 2000 review “Review of Atrazine Incident Reports, DP Barcode D270014". One of the most comprehensive reviews of atrazine was the study by Zahm et al. (1993) reviewed by HED as follows:

> Zahm et al. (1993) combined three population-based case-referent studies from Nebraska, Iowa-Minnesota, and Kansas to evaluate the role of atrazine in the development of NHL. The studies in Iowa-Minnesota and Kansas included white men, and in Nebraska, the study included both white men and women. In Nebraska, the study involved 227 white men, twenty-one years or older who had been diagnosed with NHL between July 1, 1983 and June 30, 1986. In Iowa-Minnesota, the study involved 780 white men, thirty years or older who were newly diagnosed cases with the disease between March 1981 and October 1983, and in Minnesota between October 1980 and September 1982. In Kansas, the study involved 200 white men, twenty-one years or older between 1979 and 1981. Controls were randomly selected from the same geographic areas as the cases and were matched by race, gender, five-year age groups, and vital status. An odds ratio of 1.4 was determined for the three studies combined for 101 NHL and 214 controls where atrazine was used on farms where they worked or lived. The odds ratio ranged from 1.2 in Iowa to 2.7 in Kansas. In two of the states and in all states combined, the risks were higher for farmers who used atrazine in their farming operations but did not handle the chemical than among farmers who handled atrazine. Other than atrazine, the farmers could have been exposed to other herbicides and insecticides which could have increased their chances of experiencing NHL. The study concluded that there “was little

> or no increase in the risk of NHL attributable to the agricultural use of atrazine".

To conclude that the relationship between NHL and Atrazine might be confounded by exposure to other herbicides such as 2,4-D is not the same as concluding that 2,4-D is known to be the risk factor. This association can be confounded by a number of other associations and, in any case, a full and separate weight-of-evidence determination based on all the studies would be needed to assess the carcinogenicity of 2,4-D.

Studies in Kentucky have suggested an association between county cancer rates of breast cancer and ovarian cancer and triazine exposure (Kettles et al. 1997, Hopenhayn-Rich et al. 2002). A similar study in California found various associations between atrazine and leukemia, brain cancer, testicular cancer, and prostate cancer (Mills 1998). However, these studies are subject to aggregation bias because the actual exposures of individuals in the county or how long they resided there is not known. Such studies are considered useful for hypothesis generating but not for drawing conclusions. The authors themselves warn "conclusions concerning causality cannot be drawn" (Kettles et al. 1997). Having conducted an ecologic study in Kentucky of similar design to those above, the current reviewer is very aware that agricultural pesticide use correlates with 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 (Blondell 1990).

REVIEW OF PANEL REPORT TO EVALUATE THE REPORT BY DELZELL ET AL.

In February 2002, Syngenta asked Dr. Jack Mandel (Vice President of Health and Environmental Groups, Exponent, Inc.) to convene a separate panel of epidemiologists to review the report "A follow-up study of cancer incidence among workers in triazine operations at the Novartis St. Gabriel plant". The panel was convened in early March and included Dr. Mandel and the following:
Hans-Olov Adami, M.D., Ph.D. - Professor and Chairman, Dept. of Medical Epidemiology, Karolinaka Institutet, Sweden.
Graham Colditz, M.D., Dr.P.H. - Professor, Dept. of Epidemiology, School of Public Health, Harvard University.
Dimitrios Trichopoulos, M.D. - Professor of Epidemiology, Dept. of Epidemiology, School of Public Health, Harvard University.
Vincent L. Gregory, Professor of Cancer Epidemiology, Dept. of Epidemiology, School of Public Health, Harvard University.

This panel report starts out by summarizing the prostate cancer results as follows:

> The excess prostate cancer incidence was restricted to men younger than 60 years of age and Novartis employees; indeed, among contract employees and people older than 60 years, there was no excess incidence of prostate cancer. Only 18% of the prostate cancer cases diagnosed among plant employees were not localized, compared to twice as many (37%) in the general population of LA state. Even in a large prostate cancer screening trial, the proportion of clinically advanced cancers was higher (30%) than among the workers in the Novartis St. Gabriel Plant (Koning et al. [International Journal of Cancer 97:237-244], 2000) - a reflection of the high intensity of PSA screening in the latter group.

This summary points out the importance of understanding the effect of intensive PSA screening on the pattern of prostate cancers that was observed. After providing this summary the panel provided the following "minor criticisms":
1. Expected prostate cancers were calculated on the basis of 5 year intervals rather than 1 year which could lead to some underestimation of expected cases when the incidence of the disease was rising relatively quickly, as was occurring in Louisiana up to 1996.
2. Prostate cancer incidence rates were unavailable for 1998-1999 and this could introduce more underestimation of expected prostate cancers.
3. The panel argues that the authors should have given more prominence to the comparison with the industrial corridor than with the State, because this area would be more comparable in terms of socio-economic status and health practices.
4. Reporting of cancer cases for the entire state was incomplete during the earliest part of the follow-up period and this could have led to underestimation of prostate cancer cases in the State.
5. As acknowledged by the study authors, incomplete residence

histories may have led to a relative underestimation of expected prostate cancer cases.
6. PSA screening provided by outside medical care providers was not evaluated. And the reliance on hard-copy only data for the 1989-1993 period may not have been complete.
7. The study authors reference to slight increase in several other forms of cancer is considered to be misleading because, while true, the opposite was true for other cancers. Therefore, the increases and decreases combined would be what one would expect to occur by chance.
8. The study authors noted the increase in all cancers in the subgroup with relatively long potential induction time and long duration employment. The panel stated this was misleading because it was due to prostate cancer that was heavily concentrated in the Novartis employees who worked much longer and had more follow-up than the contract workers.

HED agrees that these criticisms could be characterized as minor. The first point, about the use of a five year interval, could result in some underestimation of expected rates, but this effect was likely very small. HED disagrees with the second point. Given that rates were unavailable for 1998-99, it could mean either an underestimation or overestimation of expected cases. The third point about socioeconomic status and health practices appears logical on a superficial basis but is not backed up by any hard data. As the earlier review by Blondell (2002) noted there needs to be a more careful justification for choosing the industrial corridor which is likely to overlap the known “cancer alley” in that part of the country. The effects of points 4 and 5 would be expected to be slight at the most. In point 6, the mention of incomplete screening is likely to have at the most a minor effect given that PSA screening among workers already approached 100%. Points 7 and 8 are agreed upon by HED as noted above.

The rest of the panel review focuses on the implications of PSA screening. Autopsy studies have shown a relatively high prevalence of small prostate cancers, even among middle-aged men. Just how many of these “latent” cancers would progress to clinical disease remains uncertain, but they can be detected by PSA testing. This means that PSA likely introduces an over-diagnosis bias by detecting some latent cancers that would not have progressed to clinical disease. The panel suggests that the relatively late introduction of therapeutic interventions are unlikely to have influenced mortality statistics. Therefore, unlike most other cancers, prostate cancer mortality data may be a better indicator of incidence trends than incidence rates which are confounded by increased screening. According to the panel:

> differences in diagnostic intensity can create substantial differences in the recorded incidence of the disease. These differences would be largely limited to early stage disease with a low fatality rate and they would influence mortality rates little, if at all. While these features of prostate cancer have long been known, PSA testing as a screening tool

has amplified the consequences of differences in the intensity of surveillance.

In particular, PSA screening provides substantially longer lead time than other cancer screening tests. A detailed analysis of a large prostate cancer screening trial (Auvinen et al. 2002) suggests that PSA testing add 5-7 years lead time which could advance the time of diagnosis by up to 10-14 years compared with clinical detection. As a result, newly detected cases could exceed the expected numbers by a factor of 5 or more. In support of this effect, prostate cancer incidence in the US (SEER data) more than doubled after its introduction in the 1980s. Then the incidence declined to a level about 65% higher than during the pre-PSA screening era, as would be expected if the test were responsible for "identification of a substantial fraction of long-standing, indolent sub-clinical cases." The panel acknowledges that it is difficult to quantify the effects of PSA screening on incidence due to fragmentary data over varying time periods and the practice of measuring only single screenings but not the effects of multiple measurements for an individual. Despite these limitations and based on data from multiple sources, the panel infers that PSA screening has increased recorded incidence 2.3 times and perhaps as much as 3.5 times if those of younger age with repeated screenings are considered. Later, the panel supports the plausibility of a 5-fold increase by citing the Olmstead County, Minnesota study (Roberts et al. 1999) which found a 3.5-fold increase. HED used this same study to arrive at a similar conclusion.

The panel presents the following points as arguing against occupational exposure as explanation for the increase incidence in prostate cancer at the Novartis St. Gabriel plant:

1. There is no prior biological or epidemiological evidence that atrazine is a human carcinogen. HED agrees with this point for prostate cancer, but it should not be extended to all cancer sites.
2. "There is no established environmental risk factor that could double the incidence of prostate cancer." HED disagrees with this point. Just because an environmental factor hasn't been found before doesn't mean that the next study conducted won't find one. This is especially true for prostate cancer given the lack of careful study of environmental factors.
3. Environmental factors are known to exist based on studies of Japanese migrants, but the effects on incidence require the passage of at least a generation. This is a weak argument at best. Although some other known factor operates early in life and takes a very long time to manifest, does not preclude factors that occur later in life. Latency periods for most cancers, including prostate, are not well known with any degree of precision.
4. There is no established or suspected non-genetic risk factor that affects incidence differentially at young ages. HED agrees that one would have expected an increase at all ages. However, it is also true that the population available to study for older age groups was limited. Therefore, the power of the study to detect such an effect

was similarly limited.
5. The cancers detected at St. Gabriel were almost exclusively localized disease. There is increasing evidence that environmental factors are more likely to influence tumor progression rather than initiation. Therefore, if an effect were observed it would be less likely to be confined to localized disease. HED partly agrees, although given the absence of knowledge about initiators or promotors, far more research is needed to confirm this supposition.
6. "There was no excess of incidence from all other forms of cancer combined among the workers, reducing the likelihood that a carcinogenic factor was operating in the working environment". HED disagrees with this point. Many carcinogens are site specific and only a few are known to effect multiple sites (e.g., smoking and arsenic).

The panel conclusion reads as follows:

> Following the introduction of systematic widespread PSA testing in the Novartis St. Gabriel Plant, prostate cancer incidence has increased as much as, but no more than, would have been expected on the basis of empirical evidence and biological considerations concerning the consequences of PSA screening on reported prostate cancer incidence. There is neither a need to invoke, nor evidence to support, the contribution of environmental factors in the particular occupational setting on prostate carcinogenesis.

SUMMARY OF EXTERNAL PEER REVIEW COMMENTS

Each reviewer was supplied a copy of the original study at the St. Gabriel Plant in Louisiana, comments from the Natural Resources Defense Council (NRDC, June 3 and July 30, 2002) and a the panel report submitted by Hans-Olov Adami, Graham Colditz, Jack Mandel, and Dimitrios Trichopoulos.

1. Dr. Howard Morrison, Health and Welfare Canada

Dr. Morrison's main conclusion was "I don't think you can conclude much from the study, what little you could would be that while there was almost definitely some increased prostate cancer case finding because of increased PSA screening, there was a suggestion that this might not be the entire explanation."

While generally agreeing with the panel report by Adami et al., Dr. Morrison expressed concern that a single, underpowered epidemiologic study was not likely to find compelling evidence of an association between atrazine and prostate cancer. He cautioned that saying that PSA screening could be an explanation for the excess in prostate cancer was not the same as saying that PSA screening had been demonstrated to be the full explanation for the increase.

Dr. Morrison questioned the value of further studies of this cohort. "The proposed nested case-control study lacks any discussion of the abysmal lack of power the study will realistically have."

2. Dr. Edward Giovannucci, Harvard School of Public Health

Dr. Giovannucci limited his comments "to the question of what is the likely cause of this apparent excess of prostate cancer." His conclusion, in part, was "In my opinion, the magnitude of the increase is compatible with PSA screening as being the explanation. PSA screening advances the diagnosis time of prostate cancer by 5-10 years. Prostate cancer incidence increases sharply with age, more so than any other cancer. Thus, by advancing the diagnosis of prostate cancer by a number of years, there will be an apparent increase in the incidence of this cancer." He goes on to cite two studies which demonstrate that sharp increases in incidence can result from PSA screening. He felt this finding was further supported by the following evidence "The excess in prostate cancer was observed in active employees who received intensive PSA screening. Screening detected cancers would be expected to be asymptomatic and localized, as the vast majority were in this study. There was no indication of an increase in aggressive or advanced prostate cancers, or an increase in prostate cancer mortality."

Regarding the additional information about the exposure of the prostate cancer cases, submitted by Syngenta, Dr. Giovannucci stated that this information further supported the hypothesis that PSA screening accounted for the increase in prostate cancer. Quoting from his review:

> The additional data provided by Syngenta of the 12 prostate cancer cases in regards to cumulative index of proximity to atrazine manufacturing and on the prevalence of PSA screening further support the conclusions that the apparent increase in prostate cancer in this population is due primarily if not entirely to intensive PSA screening. Under the intensive screening for men of this age group, a large increase in the diagnosis of asymptomatic, localized prostate cancer is inevitable. The exact magnitude of increase expected is uncertain, but appear within the realms of the available data. The fact that there is no apparent increase in advanced tumors, mortality, that proximity of atrazine manufacturing did not appear to be correlated with risk, and the increase was during the years of PSA screening strongly supports the hypothesis that the excess of prostate cancer is related to PSA screening in this population.

3. Dr. Richard Hayes, National Cancer Institute

Dr. Hayes stated his principle conclusion as follows "While PSA screening may account for much of the excess of prostate cancer in this Triazine manufacturing facility, it would be premature to reject a potential role of occupational exposure to triazines as a contributing factor to the observed excess of this disease." Regarding the excess observed for other cancers, he commented "The study sample size is small, so suggestive excesses for a number of

suspect cancers, such as NHL, can not be adequately investigated."

Dr. Hayes expressed concern that atrazine might effect hormonal levels in men which are thought to have a role in prostate cancer, but acknowledged that nothing was "known about intraprostatic action of atrazine". Regarding future examination of this cohort, Dr. Hayes recommended "comparisons of exposure history of prostate cancer cases and non-cases--coupled with individual data on PSA screening--could provide insight about the reasons for the prostate cancer excess in this factory.

4. Dr. Aaron Blair, National Cancer Institute

Dr. Blair stated his principle conclusion as follows "To clearly understand the issue of prostate cancer and atrazine exposure in this cohort it is essential that a quantitative exposure assessment be added. The approach described by Breckenridge for a few of the cases is a reasonable starting point. A few additional analyses of prostate cancer risk before and after initiation of screening would also provide direct information on the impact of the screening."

Dr. Blair agreed that the report by Adami et al. (2002) "suggest that PSA screening may well explain the excess incidence of prostate cancer in this cohort. It would be helpful, however, to have more information supporting the selection of multiplication factor regarding the impact of age and other factors that might differ between a cohort of working individuals and the general population."

The additional exposure information provided by Breckenridge was criticized: "This report provides no useful information regarding the issue of atrazine exposure and prostate cancer because it only includes cases. To effectively use information about amount of exposure among the cases it is necessary to have a noncase group for comparison."

OVERALL CONCLUSION

It appears that most of the increase in prostate cancer incidence at the St. Gabriel plant in Louisiana is likely due to intensive PSA screening. The study was insufficiently large and suffered from other limitations that prevent ruling out atrazine as a potential contributor to the increase observed. On balance, however, a role for atrazine seems unlikely because prostate cancer was found primarily in active employees who received intensive PSA screening, there was no increase in advanced tumors or mortality, and proximity to atrazine manufacturing did not appear to be correlated with risk. Atrazine has been tied to inflammation of the prostate in laboratory animals and changes in testosterone levels at high doses. However, neither condition has been tied to the increased risk of prostate cancer and HED concludes the animal data do not provide biologically plausible evidence to support atrazine as a

cause of prostate cancer.

Other cancers besides prostate were found to have an elevated, though not statistically significant, increase in risk at the St. Gabriel plant. Other studies have suggested an increased risk for ovarian, breast, and other cancers, including non-Hodgkin's lymphoma. 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.

HED recommends continued monitoring of all cancers in this cohort, but does not make a recommendation regarding the special nested case-control study suggested by Breckenridge. External peer reviewers were evenly split: further study of this cohort was supported by Blair and Hayes but not by Giovannucci and Morrison.

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cc: atrazine file (080803)
Kimberly Nesci (7508C)

COPIES OF EXTERNAL PEER REVIEWS

Electronic copies provided by each of the external peer reviewers are reproduced below:

Email from Dr. Howard Morrison, Health and Welfare, Canada, December 23, 2002.

A few thoughts on an entertaining collection of reviews. You didn't have to wonder who had written what. Let me know if you would like clarifications. I don't think you can conclude much from the study, what little you could would be that while there was almost definitely some increased prostate cancer case finding because of increased PSA screening, there was a suggestion that this might not be the entire explanation.

Review of the evaluation by Adami et al.

The reviewer's conclusions are generally sound: the paper by Delzell et al. does not provide compelling evidence of an association between atrazine and prostate cancer. How likely was it for a single, underpowered epidemiologic study to do so? A perfectly reasonable explanation for the excess noted is increased PSA screening. This is not, however, to say that the study provides a "clean bill of health" for atrazine. There is a difference between suggesting a reasonable alternate explanation, and demonstrating that this explanation is the full story.

The evaluation has problems:

? "While the excess risk was confined to men below 60 years of age, there is no established or suspected non-genetic risk factor for prostate cancer that affects incidence differentially at younger ages."

A specious argument. Few epidemiologic studies report relative risks by age. Those that do typically report higher risks for younger ages, a reflection of the nature of the risk measure (multiplicative) and genetic susceptibility. See the paper: Morrison H, Savitz D, Semenciw R, Hulka B, Mao Y, Morison D, Wigle D. Farming and prostate cancer mortality. Am J Epidemiol. 1993 Feb 1;137(3):270-80 for an example of a study which linked herbicide exposure with prostate cancer (mortality), with a stronger effect noted among younger farmers.

? There is no established environmental risk factor that could double the incidence of prostate cancer.

True, but so what? There is a huge difference between saying we haven't identified strong risk factors to saying that there aren't strong risk factors.

? It isn't really fair to say that "evaluation of the prostate cancer risk by duration of employment and empirical induction period did not reveal any clear pattern...." Give the number of cases, it is unlikely to have had the power to.

? The review ignores the role of TURPs [Transurethral resection of the prostate] in the run-up in prostate cancer incidence rates in the 1980's.

? That IARC has modified it's classification of atrazine to group 3 hasn't been without controversy. See: Huff J. 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. 2002 Jul-Sep;8(3):249-70.

? To say that there is no prior biological or epidemiological evidence that atrazine is a human carcinogen is misleading. For an example of the non-existent epidemiological evidence, see: Schroeder JC, Olshan AF, Baric R, Dent GA, Weinberg CR, Yount B, Cerhan JR, Lynch CF, Schuman LM, Tolbert PE, Rothman N, Cantor KP, Blair A. Agricultural risk factors for t(14;18) subtypes of non-Hodgkin's lymphoma. Epidemiology. 2001 Nov;12(6):701-9. Many other examples of positive epidemiologic literature are cited by the review by the Natural Resources Defence Council.

Review of the evaluation by the National resources defence council

This evaluation identifies limitations to the data provided by Syngenta in their report to the EPA. The National Resources Defence Council has correctly identified the lack of exposure histories of workers as both significant and curious. It is a fair criticism to note the failure of Syngenta to model the effects of screening on incidence rates, and to wonder how Syngenta could conclude that prostate cancer cases tended to be only mildly exposed when they also claimed that they lacked information on individual employee's actual exposures.

Some of the criticisms miss the mark. It is unfortunate that the study needed to exclude more than 200 workers because they were known or presumed to have left Louisiana before 1988, however, what would the reviewer suggest? Such individuals are "lost to follow-up" and should have been censored upon being lost to follow-up.

It isn't quite fair to say that "exposure misclassification is known to bias results towards the null hypothesis" (page 21) - rather, non-differential exposure misclassification tends to bias towards the null hypothesis.

It is fair to point out that excesses were noted from cancers other than prostate. However, the numbers involved are small; I'm not sure what to make of finding 3 cases of buccal cavity cancer instead of the 2.1 expected, but it isn't much. There were cancer sites with deficits (none statistically significant), but these aren't given equal attention. This is a standard problem in epidemiology - focus on the not-statistically significantly increased associations, but ignore the not-statistically decreased associations.

The review makes much of the finding of 11 cases, when 1.2 were expected, among company employees actively working at diagnosis. This is a curious and suggestive finding, which isn't adequately dealt with in the paper by MacLennan et al.

Review of the paper: "Cancer incidence among triazine herbicide manufacturing workers."
The paper is well done, and fair, albeit somewhat conservative, in its' analysis of the data. Perhaps not surprisingly, the authors have not dealt with their failure to do an adequate job in assessing exposure histories. Nor have they discussed what is in many ways the biggest limitation of the study, that it is underpowered. Just how much could you say about dose-response when you study only has 11 cases? It also needs to be remembered that to conclude "that medical surveillance is a plausible alternative explanation of the results," while clearly true, isn't the same as concluding that this is what happened

Review of the Syngenta submission

This report is problematic.

Having an alternate explanation for the increased number of prostate cancer cases isn't the same as indicating that all of the increase was from this cause.

Why does Breckenridge say that there was a 300% risk in prostate cancer incidence reported in SEER for the US population after the introduction of PSA testing? Increases were not nearly this large. If it is for a specific sub-group, this needs to be identified.

Although it is interesting to know about the likely exposures of the prostate cancer cases are, by itself it is relatively uninformative - there are no denominator data given (and the numbers are so small...). Case in point - figure 2. How would this compare to those who weren't diagnosed with prostate cancer?

What is the point of figure 3?

Figure 6 - what does it mean to compare cumulative incidence in plant workers to SEER incidence data? It isn't a valid comparison.

The proposed nested case-control study lacks any discussion of the abysmal lack of power the study will realistically have. It would be a great study for the company to have conducted, given that it has little likelihood of observing a statistically significant effect because it will be underpowered.

Dr. Edward Giovannucci, Harvard School of Public Health, December 31, 2002

To Dr. Jerome Blondell.
From Dr. Edward Giovannucci
Re: Review of follow-up study of prostate cancer at the Novartis St. Gabriel Plant
December 31, 2002

As requested, the following is a review of the Syngenta report on the epidemiologic study of triazine workers at the Novartis St. Gabriel Plant. The study design is for the most part appropriate. A major limitation for such a study design is determining the most appropriate population rates for comparison. Two groups are used for comparison. The results suggest an increase in cancer, due mostly to prostate cancer. My comments here are limited to the question of what is the likely cause of this apparent excess of prostate cancer. I do not consider other potentially relevant data such as animal or mechanistic studies in this review.

The major question is whether the excess rates are due to an occupational exposure, are compatible with chance, or are due to another factor. These findings are not likely due to chance. Besides occupational exposure, the most likely candidate for an alternative explanation is a high frequency of PSA screening, the diagnostic test that detects prostate cancer. The notable fact about this study is that the time period overlaps with the availability of the PSA test in the United States. Prostate cancer is unique in that the vast majority of pathologic cancers would not come to clinical notice except for sensitive diagnostic tests, such as PSA. When PSA began to be used in the United (and other areas), the diagnosis of prostate cancer increased dramatically. There is no credible evidence that there was a true increase in incidence as mortality has been relatively stable or even decreased. Thus, the use of the PSA test can definitely cause a remarkable substantial increase in prostate cancer.

Given the extraordinarily high prevalence of PSA screening in the active Novartis employees (98% had at least one PSA test by age 45 years), an excess of prostate cancer would be expected. Several facts indicate that the excess of prostate cancer was related to PSA screening:

- The excess in prostate cancer was observed in active employees who received intensive PSA screening.
- Screening detected cancers would be expected to be asymptomatic and localized, as the vast majority were in this study.
- There was no indication of an increase in aggressive or advanced prostate cancers, or an increase in prostate cancer mortality.

Given the localized, asymptomatic nature of the tumors, the majority were clearly detected through PSA screening. The remaining question is whether this excess is consistent with what would be expected through PSA screening alone, or if the data suggests an additional etiologic factor accounting for an increase in risk. In my opinion, the magnitude of the increase is compatible with PSA screening as being the explanation. PSA screening advances the diagnosis time of prostate cancer by 5-10 years. Prostate cancer incidence increases sharply with age, more so than any other cancer. Thus, by advancing the diagnosis of prostate cancer by a number of years, there will be an apparent increase in the incidence of this cancer. For example, in one study, the ratio of prostate cancer incidence in men who were screened with PSA was 6.5 times higher than the control group. In essence, there were 6.5 times more prostate cancers diagnosed due solely to PSA screening (BJU International 2001;88:811-17). In a screening trial in a Finnish population, the ratio of the number of cases detected through PSA screening in the first year relative to the number expected based on age-specific incidence rate in Finland was 14.4 for men aged 55 years (Cancer Causes and Control 2002;13:279-285). This ratio of screened detected cases to unscreened population incidence increased with age so the potential bias in men aged younger than 55 years would be even greater based on these data. 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.

The additional data provided by Syngenta of the 12 prostate cancer cases in regards to cumulative index of proximity to atrazine manufacturing and on the prevalence of PSA screening further support the conclusions that the apparent increase in prostate cancer in this population is due primarily if not entirely to intensive PSA screening. Under the intensive screening for men of this age group, a large increase in the diagnosis of asymptomatic, localized prostate cancer is inevitable. The exact magnitude of increase expected is uncertain, but appear within the realms of the available data. The fact that there is no apparent increase in advanced tumors, mortality, that proximity of atrazine manufacturing did not appear to be correlated with risk, and the increase was during the years of PSA screening strongly supports the hypothesis that the excess of prostate cancer is related to PSA screening in this population.

Please contact me if you have any questions.

Sincerely.

Edward Giovannucci, M.D. Sc.D.
Associate Professor of Medicine
Harvard Medical School
Associate Professor of Nutrition and Epidemiology
Harvard School of Public Health

Dr. Richard Hayes, National Cancer Institute

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January 8, 2003

Jerome Blondell, Ph.D., M.P.H.
Health Effects Division (7509C)
U.S. Environmental Protection Agency
Washington, D.C. 20460

Dear Dr. Blondell,

Please find attached my review of the materials related to the epidemiologic study of triazine workers at the St. Gabriel plant in Louisiana.

If you need further information, please do not hesitate to ask.

Sincerely yours,
Richard B. Hayes, DDS, PhD
EPS 8114
Division of Cancer Epidemiology and Genetics

[attachment]

The “Follow-up Study of Cancer Incidence among Workers in Triazine-related Operations at the Novartis St. Gabriel Plant” included 2,045 subjects identified from Novartis employment records at the St. Gabriel plant, including for study workers who had accrued at least six months of employment in the plant by 1992 and had worked at anytime since 1970 in jobs with potential exposure to triazines (based on job location). Study subjects included three broad categories of worers: company employees working at anytime since 1970, contract production employees working anytime since 1977, and contract maintenance employees working anytime since 1983 (i.e., earliest years for which work records were available for individual employees). Exit date from Louisiana (LA) was determined through tracing for almost all subjects. Cancer incidence was based on linkage, using appropriate identifiers, to LA cancer incidence and mortality files, and was calculated to date of specific cancer occurrence, date of death, to end-of-follow-up, 1997, or to the estimated date of emigration from the State, whichever came first.

Cancer incidence was evaluated during 1985-97 showing no overall

increase in cancer, however, a statistically significant excess of prostate cancer was found (11 observed, 4-6 expected); the excess was restricted to men less than 60 years of age and was found mostly among active Novartis employees. Further follow-up through 1999 found 17 cases, yielding a 6 to 9-fold increase above the expected prostate cancer rate. It is noteworthy that prostate cancer cases were largely limited to workers who had been hired at least 10 years prior to disease development, allowing for a potential latency time, however, duration of work was not clearly related to excess risk. Active PSA testing of non-symptomatic men began about 1992. Five of the prostate cancer cases occurred before this date and 12 afterwards. Fourteen cases were localized, 3 were not (by time period?) Mortality data showed 1 prostate cancer death and 0.5 expected.

The study was well designed. Appropriate procedures were used to identify study subjects. The follow-up procedures for determining vital status and cancer occurrence while resident in LA are adequate. The use of the LA cancer registry and death certificates for case identification is appropriate. The use of local population rates of cancer is a standard approach. The decision to censor follow-up at time of emigration from the State is defensible; the proportion of subjects censored due to this is relatively small and it is unlikely that risk estimates were substantially biased by this procedure.

The study does have limitations. The study sample size is small, so suggestive excesses for a number of suspect cancers, such as NHL, can not be adequately investigated. Exposure data is inadequate to assess a relationship between occupational exposure to triazines (or other agents in the study facility) and cancer risk. Relationships with duration of employment are difficult to interpret because it is unknown how exposures varied over time. While a high rate of PSA screening since 1993 among active Novartis employees may account for much of the prostate cancer excess, the study does not provide quantitative estimates of such an impact. Further analysis of risk by calendar period, comparing PSA screening *vs.* non-screening time-periods, could provide some insight into this important issue. Risks are unknown for the time period prior to 1985.

Aside from increased risk associated with increasing age, race, and family history of prostate cancer, the causes of this disease are uncertain. Steroidal hormones are believed to play a role because of their importance in prostate development, prostate cancer management, and their successful use in experimental disease induction. While testosterone and its metabolites are the prime suspects, inter-relationships in prostate carcinogenesis with estrogenic compounds may also be important. Atrazine and related compounds have profound estrogen disrupting capacity in amphibians at a very low dose (Hayes TB et al. PNAS 99:5476-5480, 2002). IARC judged the evidence on the carcinogenicity of atrazine to be sufficient in animals but inadequate in humans (IARC Monographs, Vol. 73, 1999). There is virtually nothing known about intraprostatic

action of atrazine and related compounds and the few other epidemiologic studies on triazine-related prostate cancer risk in humans are not informative, due to study design limitations.

Conclusion: While PSA screening may account for much of the excess of prostate cancer in this Triazine manufacturing facility, it would be premature to reject a potential role of occupational exposure to triazines as a contributing factor to the observed excess of this disease.

Future studies: Recently, Syngenta carried out a limited exposure assessment for most of the prostate cancer cases. Did this assessment cover worker exposures from the beginning of employment—prior to 1970? Quantitative exposure information was not used (and is apparently not available), so the exposure scoring is on a qualitative scale. Although limited, comparisons of exposure history of prostate cancer cases and non-cases--coupled with individual data on PSA screening--could provide insight about the reasons for the prostate cancer excess in this factory. In designing such a study, I would not match at a 4:1 ratio on PSA and other factors, as suggested in the Exponent, Inc. proposal, as questions will always remain about the suitability of the matching choice in this small study. With only 2,045 subjects, all could be included or a random sample of some 20%, allowing for reconstruction of risks to the full cohort.

Dr. Aaron Blair, National Cancer Institute

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December 23, 2002

Jerome Blondell, Ph.D.
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U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington, DC 20460

Dear Dr. Blondell:

I have reviewed the additional documents regarding the "Follow-up study of cancer incidence among workers in triazine-related operations in the Novartis St. Gabriel plant" as you requested. My comments are below:

Evaluation by Adami, Colditz, Mandel, and Trichopoulos:
These scientists were hired by Syngenta to evaluate the Delzell report with specific instructions to "focus on understanding the impact of screening associated with prostate specific antigen testing." My comments regarding their review are below.

Page 3 - The authors note that there "may have been biases that could have led to underestimation of expected number of prostate cancer cases". This is correct, but there are also a number of biases that might lead to an underestimation of relative risk, particularly in the area of exposure misclassification. This can have profound effects on estimates of relative risks.

- I do not think the comment that "the change in incidence requires the passage of at least one generation" regarding migration is correct. For prostate and a number of other cancers, the rates change within the migrant's lifetime.

- It is true that there is no established prostate cancer risk factor that is known to affect incidence differentially by age. However, there are very few risk factors known, so this is not surprising.

Page 6 - It seems to me the incidence pattern is a bit more complex than described here. The authors say that the entire cancer excess (5 cases from 46 observed versus 41 expected) is entirely explained by the prostate cancer excess (which is 11 - 4.5 = 6.5). It is also correct to say that all cancers except colon, lung and breast in Table 7 have a larger observed than expected number. Prostate could account for the small excess, but so could other combinations of sites. In Table 7 if you add the observed and expected number for the specific cancers listed, i.e., everything but “Other” you get 37 observed and 29.7 expected. This means that for the “Other” there are 4 observed and 11.3 expected. This is about what one would expect for a cohort where the overall cancer rate is about 1.0, i.e., some sites with SIRs above 1.0 and some below, but without other information it is not appropriate to single out one cancer as explaining the excess or deficit.

- The proportion of localized prostate cancers is an important indicator of the effect of screening. The higher rate in the cohort than the general LA population suggests a screening effect. There is some difference in the proportion of prostate cancer that is localized by age, and it was not clear if the authors took this into account in this comparison.

Page 7 - It is suggested that use of 5-year age groupings would underestimate the expected number of cases. This is probably true, but without some quantification of the magnitude of this effect, it is difficult to evaluate its impact. It is likely to be small.

- Incidence rates were not available for the years 1998 and 1999. With rising prostate cancer rates this could also underestimate the expected number. Again the impact is likely to be small because the greatest affect of screening on prostate cancer was in the early 1990s. This problem can be eliminated through analysis of cancer incidence in the cohort only through 1997.

Page 8 - The authors state that since the prostate cancer excess can account for the total cancer excess and, therefore, the comment on excesses for other cancers by Dr. Delzell is “unintentionally misleading.” It would seem that this comparison could also be turned around. The excesses for some other cancers can account for the total cancer excess. It is unclear why it should only be viewed from the prostate cancer perspective.

Page 9 - The authors say that “small, histopathologically malignant, lesions in the prostate among middle-aged and particularly elderly men” are very high. It was my impression that this applied only to elderly men. Nonetheless, it underscores the reason why screening for prostate cancer may

uncover malignant lesions that would not necessarily progress to diagnosis under normal conditions.

Page 20 - The authors provide a useful procedure to estimate the number of prostate cancer cases that might be due to the company PSA screening. It seems reasonable that repeat screening would increase the number of cases identified, but this would surely have diminishing returns. It was my impression that Auvinen recommended that screening did not need to take place every year. This would indicate that each repeat year identifies fewer cases. The authors appear to have taken this into account, but it was not entirely clear to me. More information on how the authors arrived at the value for X of 3.5 would be helpful, since it is this value that is critical for determining if screening can explain the excess cases at the plant.

Page 21 - The authors state that environmental factors may have profound effects on prostate cancer incidence, but these “factors are likely to operate early in life.” However, later they say that “there is growing evidence that external factors may have a stronger influence on advanced, rather than earlier, stages of the natural history of prostate cancer.” These points seem contradictory.

The review by Adami et al. provides useful information to evaluate the impact of company PSA screening on the prostate cancer incidence rates in the cohort. They estimated the number of cases likely to occur from the PSA screening using information from the literature. This is an appropriate approach. The results suggest that PSA screening may well explain the excess incidence of prostate cancer in this cohort. It would be helpful, however, to have more information supporting the selection of multiplication factor regarding the impact of age and other factors that might differ between a cohort of working individuals and the general population.

Summary Information by Charles Breckenridge:
This document provides information on atrazine exposure for some of the prostate cancer cases in the Delzell report. This report provides no useful information regarding the issue of atrazine exposure and prostate cancer because it only includes cases. To effectively use information about amount of exposure among the cases it is necessary to have a noncase group for comparison. If it is possible to reconstruct possible atrazine exposure for cases, as was done for this report, it could be done for controls also. This would be helpful, although the small number of cases would be a severe limitation.

National Resources Defense Council (NRDC) Comments:
The NRDC raises a couple of methodologic issues about the cohort. They note that more than 200 workers were excluded from the study because they presumedly left Louisiana before 1988. This is

appropriate because the time frame for the cohort follow-up was 1988 through 1997. They are correct that if these workers had longer or heavier exposure the results might have been different, but this is always the situation. A cohort can only make clear statements about the exposures being studied. A second point was that contract workers with lower levels of exposure were included and this could lower relative risks because of exposure dilution. This could also be true, but it is not a bias in the study, however it does limit extrapolation of study results to other scenerios. Both of the NRDC points underscores the absolute necessity of performing an atrazine exposure assessment in the study.

Conclusion: To clearly understand the issue of prostate cancer and atrazine exposure in this cohort it is essential that a quantitative exposure assessment be added. The approach described by Breckenridge for a few of the cases is a reasonable starting point. A few additional analyses of prostate cancer risk before and after initiation of screening would also provide direct information on the impact of the screening.

Please feel free to contact me if you have questions.

Sincerely,
Aaron Blair, Ph.D.
Chief, Occupational Epidemiology Branch