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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

March 25, 2002

MEMORANDUM

SUBJECT: Review of Atrazine Cancer Epidemiology Studies:
"A Follow-up Study of Mortality Among Workers at the Novartis St. Gabriel Plant"
"Follow-up Study of Cancer Incidence Among Workers in Triazine-related Operations at the Novartis St. Gabriel Plant" both by Elizabeth Delzell et al.
DP Barcode D281568, MRID# 451521-01 and 455184-01, Chemical #080803

FROM: Jerome Blondell, Ph.D., Health Statistician
Chemistry and Exposure Branch 1
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THRU: Francis B. Suhre, Senior Scientist
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TO: Catherine Eiden, Senior Scientist
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BACKGROUND

This review updates an earlier version of this review dated December 13, 2001 (DP Barcode D278933, MRID# 455184-01) to incorporate two external peer reviews and to include an earlier mortality study of the same St. Gabriel Plant in Louisiana.

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 recent published studies concerning atrazine. The earlier review by Blondell (September 13, 1996) had the following conclusion:

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> 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 current studies submitted by Novartis did not find additional evidence of risk of NHL, but focus principally on a statistically significant increase in prostate cancer. As the review below notes, this finding may be accounted for by a very intensive screening program for prostate cancer at the plant which may be responsible for the apparent increase in risk.

REVIEW

The mortality analysis (MRID#451521-01) includes 2,213 workers and a total of 32,473 person-years of observation for the time period 1970 through 1997. There was no statistically significant increase for any form of cancer. As in the earlier review, there were 3 deaths from non-Hodgkin's lymphomas which was non-significant and were not related to increasing years since hire or with years worked at the plant. The same conclusion reported above for the earlier study also applies to this report. Therefore, the remainder of this review will be devoted to the incidence study (MRID#455184-01) which does offer new findings.

The most recent version of the morbidity (incidence) study at the St. Gabriel plant in Louisiana includes a larger number of workers and a longer period of follow-up (21,200 person-years of follow-up and a median of 12.6 years per subject). The current study provides analysis on cancer mortality and incidence at the plant among employees and contract workers for the time period 1985 through 1997 (though the incidence analysis includes two additional years, 1998-1999). A total of 2,045 subjects meant the criteria for being in this study. Subjects had to have worked at least six months prior to 1993 to be included in the study. Subjects had to have some exposure to

triazines or their precursors to be included in the study.

Mandatory reporting of cancer cases was established in Louisiana starting in 1983. According to study authors many of the cases reported in the first two years may have been prevalent cases (diagnosed prior to 1983) instead of incident cases. Therefore, only cases reported to the Louisiana Cancer Registry after 1985 were included in the study. Reportedly, the registry did not expand to cover the entire state until 1988, however, the region around the plant was known to have "reasonably complete and accurate reporting" of incident cases starting in 1985.

Subjects had to have at least six months at the plant by the end of 1992 to be included in the study. In addition, they had to work in production, maintenance, laboratory or other jobs involving potential exposure to triazines or their precursors. Eligible for consideration were Novartis employees employed since 1970, contract production employees employed since 1977, or contract maintenance employees employed since 1983. To be eligible employees had to live in Louisiana since 1985 and work in the plant during the 1970 to 1992 time period. Subjects were selected from those enrolled in an earlier mortality study which totaled 2,213. Of these 2,045 meant the criteria listed above for inclusion in the incidence study. A total of 757 of these were Novartis employees, 687 were contract production workers, and 601 were contract maintenance workers.

Extensive follow-up with a variety of data sources was performed to identify the location and vital status of potential study subjects. The authors have provided good documentation of their efforts to track all subjects and there were very few subjects lost to follow up. In addition, careful effort was made to be sure that data on morbidity and vital status was collected in the same manner so there would not be bias in case ascertainment. Where differences existed, additional analyses were often performed to assure that these differences did not explain differences in the study results. This was especially true for residence history and authors performed careful analyses to assess the quality of this data and its impact on study results.

The employee had to have a diagnosis during the 1985 to 1999 time period to be considered a cancer case. Initial analyses were restricted to just those cases diagnosed from 1985 through 1997. During this more restricted time period, there were 46 cancer cases compared to 41 expected for a standardized incident ratio (SIR) of 113 with a 95 percent confidence interval of 83 to 151 (not statistically significant). A SIR of 100 would mean the number of deaths observed is equal to expectation in the comparison population implying no increased risk from exposures in the plant. Two comparison populations were chosen for this study: the State of Louisiana and the subpart of the State referred to as the "Industrial Corridor," the region where the plant was located. This region consisted of seven 'parishes' (Louisiana is the only state that has parishes instead of counties). The earlier mortality study has chosen the U.S. population and the State of Louisiana as comparison populations. Justification for using only the region around the plant as a comparison was not noted. Presumably, it was thought that other exposures and lifestyle factors, outside the plant, might be influencing cancer rates and therefore the local region might serve as a better control. On the other hand, the heavily industrialized region of Louisiana has long been known as a high cancer area, leading to the area being characterized as "cancer alley." It would not be appropriate to compare

cancer rates with other nearby populations that high cancer rates if those rates were due to other chemical exposures. Such a comparison with a known high cancer area should be carefully and stringently justified which was not the case in this report.

The non-statistically significant increase in non-Hodgkin's lymphoma found in the earlier study of this cohort (reported in the conclusion above) has not changed. No new NHL cases have been reported, so the increase is slight (SIR =129, 95% confidence interval 27-378). The only statistically significant finding for cancer specific sites was for prostate cancer. This review like the report will focus almost entirely on those findings. Comparisons reported below will are made with the State of Louisiana, not the industrial corridor. However, both results will be reported in those instances where statistical significance differed between the two comparisons.

The initial comparison was based on cases occurring from 1985 through 1997 when there were 11 prostate cancer cases. This resulted in a SIR of 247 (95% confidence interval 123-443) when compared to the State and a SIR of 175 (non-significant, 95% confidence interval 87-312) when compared to the industrial corridor. Note that the authors appropriately computed ratios taking into account race, age, and calendar time period specific rates of the Louisiana State population or the industrial corridor subregion. Additional analysis was performed to determine whether possibly incorrect assumptions about residence history might have influenced the results. Analyses were also performed to determine what influence years since first hire and year worked had on the results. These analyses are done to take into account cancer latency period and possible effects of longer duration of exposure. In general, the statistically significant finding for prostate cancer persisted across the various subcategories of analysis.

Ongoing medical surveillance of plant employees found an additional six prostate cancer cases in 1998 or 1999, after the end of the 1985-97 study period. A supplemental analysis was performed to assess this most up-to-date information. However, to compute expected numbers in the comparison population, the authors had to use 1995-96 figures to estimate expected numbers for the State in 1995-99 and 1995-97 figures to estimated expected numbers for the same time period for the industrial corridor. Based on a total of 17 prostate cancers, the SIR was 255 which was statistically significant (95% confidence interval, 148 to 408). Most of this increase was due to Novartis employees which accounted for 14 of the 17 cases (SIR = 364, 95% confidence interval 199 to 610). Contract production and contract maintenance workers accounted for only three prostate cancer cases with SIRs of 119 and 101, respectively and not statistically significant. Novartis employees tended to be older and worked much longer at the plant (median, 10.6 years) than did the contract employees (median 1.4 for contract production and 2.5 for contract maintenance employees). The main question for this study is whether the statistically significant increase in SIRs for Novartis employees reflects their greater exposure or the increase medical screening provided for plant employees (PSA testing starting at age 40). Analyses were also performed by age group as shown in the tables below:

Table 1. Standardized incidence ratio and 95% confidence interval for all workers compared to the Louisiana State population, 1985-1999.

All Workers		Age < 50 years		Age 50-59 years		Age 60+ years	
SIR	95% C.I.	SIR	95% C.I.	SIR	95% C.I.	SIR	95% C.I.
255	148-408	671	218-1566	391	195-699	32	1-179

Table 2. Standardized incidence ratio and 95% confidence interval for all workers compared to the industrial corridor population near the plant, 1985-1999.

All Workers		Age < 50 years		Age 50-59 years		Age 60+ years	
SIR	95% C.I.	SIR	95% C.I.	SIR	95% C.I.	SIR	95% C.I.
178	104-285	398	129-930	266	133-477	24	1-134

Note that the choice of the Louisiana State population or the industrial corridor population near the plant did not change whether results were statistically significant. Though in all cases the ratios for the industrial corridor comparison were lower than those for the Louisiana State population. For most cancers, including prostate cancer, older ages are at higher risk. Therefore, it is of special concern to find that the highest risks found in this study were among the younger workers, less than 50 years of age. On the other hand, the lack of increased risk in the 60 plus age group is consistent with the absence of active employees and a much lower rate of PSA screening among those who had left the plant and were no longer eligible for free screening. Among the 14 prostate cancer cases occurring among Novartis employees, the ages ranged from 44 to 58 years at diagnosis with a median of 51 years.

Analyses were also performed on the basis of years since hire and by years worked. All but one of the observed prostate cancers occurred in men with 10 or more years since hire, however, these were almost exclusively Novartis employees who were subject to intensive PSA screening for prostate cancer. Among these Novartis employees (with 10 or more years since hire) those who worked at the plant less than five years had a SIR of 365 (based on two cases observed and 0.6 expected, not statistically significant) and those who worked five or more years had a SIR of 384, (based on 12 cases observed and 3.1 expected, and statistically significant). One would have expected a higher SIR for those with more years worked at the plant if carcinogenic exposures were responsible for this increase, however, given the small numbers in these subgroups, it is important to be cautious about over interpretation of these results.

PSA screening to detect prostate cancer was offered to Novartis employees beginning in 1989. Starting in 1992, PSA testing was offered to all men 50 years of age and older and to younger men at the plant physician's discretion. Then, in 1994, employees were offered a digital rectal examination to all men 40 years of age or older and PSA screening to men 40-44 years with a family history of prostate cancer or if African American, and to all men 45 years or older. As a result, from 1993 to 1999, 90-100% of active Norvartis employees 45 years or older received a PSA test and 33-37% of those ages 40-44 years after 1994. Given this extraordinary high rate of screening, might screening alone be responsible for the significant excess of prostate cancer that was primarily observed among the Novartis employees? Nine of the 14 Novartis employees had medical records indicating whether they were symptomatic or not and all nine were asymptomatic, indicating that the PSA screening was responsible for the early detection of these nine cancers.

A principal source of confusion in this study is the measurement, or lack thereof, of exposure to atrazine or its precursors. Earlier reports on this study made it quite clear that subjects had to have some exposure to triazines or their precursors to be included in the study. The study summary notes:

> We did not directly examine the relation between workplace exposures and prostate cancer incidence because detailed job histories were unavailable for many subjects, and comprehensive historical biomonitoring and industrial hygiene data were lacking. The plant collected urine samples from employees and analyzed them for triazine metabolites since 1982. However, testing was done mainly for workers in triazine packaging and formulation areas.

Then, the results section notes that eight of the 14 prostate cancers among Novartis employees worked principally as "chemists, engineers, or supervisors or as operators in areas that would have entailed sporadic, if any, exposure to atrazine." The phrase "if any" implies that some employees with prostate cancer might not have had any exposure which contradicts the criteria for inclusion. The information on these eight goes on to note that their work histories did include exposure to "cyanuric chloride, hydrogen cyanide, process engineering, engineering services, technical control and chemical development." This provides qualitative evidence that exposure to chemicals other than the triazines might have been responsible for some of these prostate cancers. But there are no quantitative measures to back up this suggestion. With all the effort put into the follow-up of these workers, it is difficult to understand why more hasn't been done to fully assess exposure, either through biomonitoring, job histories, or questionnaire of subjects, most of whom are still alive and available for questioning (though admittedly, some, reportedly involved in law suits against the company, would be unlikely to cooperate). Page 47 of 170 of the study states "We did not have data on individual subjects' exposures to atrazine or other chemicals," which would seem to contradict an earlier statement that urine samples were taken from workers in the packaging and formulation areas since 1982. The appendix notes that urine was tested for cyanuric acid which could also result from exposure to other chemicals and therefore not a specific indicator for atrazine or triazines alone. However, later data for 1991-1998 measured diaminochlorotriazine in the powder packaging areas. A greater accounting of the urine and dust air measurements should be considered even though this data was limited to certain employees and time periods. The authors state: "The historical exposure data, however, may be useful in a nested case-control study. Such a study would need to obtain

detailed plant work histories of individual subjects; develop a work area/job-exposure matrix (JEM) using multiple information sources . . . " Such an approach is recommended by the current reviewer. The lack of significant follow-up to determine employees' relative exposure is a major weakness of the current study.

Based on five observed cases, workers in this age group had a prostate cancer incidence that was 6.7 times higher than the Louisiana State population (95% confidence interval was 2.2 to 15.7 times higher) and 4.0 times higher than the industrial corridor (95% confidence interval was 1.3 to 9.3 times higher). To support the suggestion that PSA screening may be responsible for the statistically significant increase noted in the present study, the authors point out that other studies have noted a very marked increase (up to threefold in one instance) in prostate cancer from 1987 to 1992 as screening became more widespread. However, this is somewhat contradicted by a decline observed after 1992 when, presumably PSA screening was still increasing or at least stable. A brief look at other studies by this reviewer confirms that PSA screening has been accompanied by increasing trends in prostate cancer incidence, but there appears to be a lack of quantitative data to say just how much increase in prostate cancer should be expected with a given amount of increased PSA screening. For this reason, an external review was requested by an expert in prostate cancer epidemiology (Dr. Giovannucci) who was asked to specifically address this question.

Note that the review completed above was prepared independently without examining the two external peer reviews that were requested. The information that follows summarizes the results of these reviews and incorporates their findings into the conclusion.

External reviews

Dr. Edward Giovannucci, of the Harvard Medical School and Harvard School of Public Health reviewed the excess prostate cancer incidence in Novartis employees and concluded "there is no feature of the data that leads me to suspect that the apparent increase is nothing more than intense PSA screening in the Novartis employees. Under such intense screening men of this age, a large increase in the diagnosis of asymptomatic, organ-confined tumors would occur with almost certainty. The expected magnitude of such an increase cannot be known for certain, but this observed increase appears well within the realms of what would be expected with increased detection."

Dr. Aaron Blair, Chief of the Occupational Epidemiology Branch of the National Cancer Institute provided a review of the current study. He was particularly critical of the absence of work histories for Novartis employees which he felt were essential to fully evaluate the cancer incidence in relation to the exposure to atrazine. He argued that the company should have provided the investigators "with complete work histories of the workers and asked the investigators to perform full-blown, state-of-the-art exposure assessment." He questioned whether some of the non-significant excesses reported might represent an effect of occupational exposure. He noted that with additional information, some of the non-significant increases might be more closely tied to an occupational exposure in a specific subgroup of employees. Absent this more detailed analysis, he did not draw any conclusions about the likelihood of any particular cancer and atrazine exposure.

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Conclusions

This study did find a significant association between prostate cancer and working at the St. Gabriel plant were 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.

Attached: External Reviews

cc: Correspondence
atrazine file (chemical no. 080802)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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November 14, 2001

Jerome Blondell, Ph.D.
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Dear Dr. Blondell:

I have reviewed the document "A 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:

General Comments:
The authors report a small, overall cancer excess. This is derived from a significant excess of prostate cancer and from non-significant excesses for cancers of the buccal cavity, esophagus, stomach, bladder, thyroid, and lymphatic and hematopoietic system. The overall cancer excess is somewhat surprising because many retrospective cohort studies show a deficit of cancer overall because of the healthy worker effect. The numbers for most specific cancers are small and confidence intervals wide. This introduces uncertainty regarding interpretation of the data regarding specific sites. One would not expect chance, however, to go heavily in one direction, i.e., all toward excesses. Consequently, I view the excesses for these cancers of considerable interest.

The authors have performed a number of actions and analyses to provide useful information regarding interpretation of these findings. The information on proportion of workers receiving company-sponsored PSA tests by calendar year is useful, as is information on stage of disease for prostate cancer to assess the possibility that the excesses are due to the screening. It would have been informative to perform analyses to directly evaluate these influences or perform calculations to quantitatively estimate the magnitude of the impact from screening on the SIRs. The major limitation of the study was the lack of detailed work histories on study subjects. The document suggests that these were available for Novartis employees. Since work histories are so critical to the evaluation of specific exposures and disease, it seems a major omission not to obtain them. The company have these data and the personnel to help the investigators evaluate them. A an occupational study without such a component would not peer review anywhere.

Specific Comments:
Page iv - The document indicates that 8 of the 14 cases of prostate cancer worked only in jobs that would have had little exposure to atrazine. Throughout the document, however, the authors have stressed that work histories were not available. So where did this

information come from on jobs held by the cases. If available it should have been analyzed in a standard fashion. As presented here it is numerator data and is largely unusable and potentially misleading. There must be some comparison group to make any sense out of it at all.

Page v - It is interesting that the study did not include an effort to get work histories and evaluate exposure, yet this is used as an explanation as to why the excesses should not be meaningful.

If urine was monitored for triazine levels it would be useful to have these data presented. It would be relevant to some of the members of this cohort.

Page vi - The summary says "no toxicologic study has identified effects on the prostate after adult exposure to triazines." No references to such studies were provided? Are there such studies, or is it that no evidence is available?

Page 4 - What is the evidence that the registry coverage in the region of LA where the plant was located was "reasonably complete" in 1985?

Since this was a study sponsored by Novartis it is surprising that work histories were not obtained to develop an exposure classification system. This is pretty much the standard approach in all occupational cohort studies now days. It should have been a relatively easy process for the company to provide this information. Any serious effort to evaluate occupational exposures should have included at least a qualitative effort at exposure assessment. The failure to focus on specific exposures usually dilutes the risk estimates because workers with no important exposures are included with those with potentially hazardous substances. The fact that there is an excess of prostate cancer and other cancers in the entire cohort suggests that the relative risks may be even larger for subgroups with specific exposures.

Page 28 - It is suggested that the Novartis prostate screening, which became commonplace in 1993, might have contributed to the excess of prostate cancer. A useful analysis to evaluate this issue would be to look at SIRs for prostate cancers occurring prior to 1993 and those occurring after 1993, when the screening became commonplace.

Page 32 - I am not sure that it is correct to say that the overall cancer excess is mainly due to the prostate cancer excess. If you add up the excess cancers for the sites that have SIRs greater than 1.0, the other cancers have a larger number of excess cancers than prostate cancer.

With information on PSA testing by Novartis and estimates of the prevalence of this activity in the general LA population, it would be possible to estimate the excess

number of prostate cancers likely to be due to the screening. This would be preferable to simply stating that it might have an effect with no quantification of the magnitude.

Page 35 - A useful analysis would be to compare short-term and long-term workers who underwent PSA screening at Novartis. This would eliminate the impact of the screening, since all workers in the analysis would have been screened, and it would still allow the evaluation of a possible role for occupational factors.

Nine of the 12 prostate cancer cases with information from medical records were asymptomatic. What is the expected number for asymptomatic prostate cancers? This is needed to determine if extra cases were identified by the screening. It is also important to note that the PSA screening would not explain the excesses for the other cancers.

Page 36 - It is likely that the mammary tumors in one strain of rats occur from a mechanism that is not relevant to humans. This does not necessary imply, as the document indicates, that atrazine is not an endocrine disruptor in humans. Atrazine does have hormonal properties and could impact cancers other than breast in humans.

The discussion of studies of the mortality from prostate cancer among workers exposed to atrazine is used to support the contention that the prostate excesses in this study are probably not related to atrazine. These mortality studies are quite weak. The numbers for the cohort study are very small (3 observed deaths) and the potential for exposure in the ecologic study is problematic.

Page 37 - I find it a little surprising that the lack of information on individual's exposure to atrazine is used as a argument that the excesses observed may not be important. It would seem the company should be able to provide such data for their employees. The text does indicate that half of the cases worked as supervisors or in technical jobs and should not have had much exposure. This issue is, of course, what would be the distribution on noncases in such jobs. If work histories were not available, how is it known that these cases worked in nonexposed jobs?

Page 38 - The reduction in SIRs when the industrial corridor population is used is not large and clearly well within the confidence interval for the SIR using the general population.

Page 40 - It is indicated that no ovarian cancers were observed. How many were expected? The lack of cases is not of much value without the expected number.

Summary:

I found the excess of prostate cancer and several other cancers in this cohort quite interesting. I was surprised, however, about the poor quality of the study regarding exposure assessment. The authors did as much with the data as they could, but given the importance of the issue clearly the

company should have provided them with complete work histories of the workers and asked the investigators to perform a full-blown, state-of-the-art exposure assessment. The lack of detailed information on work place exposure, however, does not diminish the interest in the cancer excesses observed. In fact, it may increase the concern. This increased interest occurs by seldom do we find all exposure subgroups in a plant to have similar disease risks. Usually the excess resides in some specific exposure group. This suggests that if there is an occupational component contributing to the excesses observed here, it is highly likely that the burden is not spread evenly across the plant population. Consequently, there may be some specific subgroup at even higher risk than suggested here.

Sincerely,

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December 18, 2001

Jerome Blondell, Ph.D., MPH
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Dear Dr. Blondell:

As you requested, the following is my review of the final report "A follow-up study of cancer incidence among workers in Triazine-related operations at the Novartis St. Gabriel Plant," by Delzell et al.

This study reports an excess of prostate cancer incidence in Novartis employees compared to expected rates based on external populations. This increase occurred during the time period that PSA screening became widely available in the United States. In particular, Novartis male employees received intense PSA screening. A number of factors indicate that intense screening for the male employees accounted for this apparent increase in prostate cancer. These factors are summarized here:

(1) Many studies indicate that the apparent incidence of prostate cancer is largely dependent on screening and diagnostic practices. For example, mortality rates have remained relatively constant whereas incidence has gone up multiple-fold as screening and diagnostic techniques have increased in availability. As reviewed in the report, many databases support this large increase in diagnosed prostate cancer.

(2) The excess prostate cancer was seen mostly in active Novartis employees, who received intense PSA screening. The proportion of these men who had at least one PSA test by age 45 was 98%. This is extraordinarily high, and likely exceeds that in the comparison population. Clinicians would not typically screen men in their forties unless there was a strong family history of prostate cancer. Recommendations are usually for screening beginning at age 50.

(3) The relative magnitude of a bias would be expected to be higher for relatively young men because their rates are generally low and screening is lower than for older men whom physicians perceive to be at high risk for prostate cancer. Thus, the detection of some additional cases could make a large impact on relative rate measures.

(4) All characteristics of the tumors were consistent with heightened detection, including their being asymptomatic and localized to the prostate.

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(5) While there are not direct data to evaluate what the proportion of men this age would be expected to have latent prostate cancer, autopsy studies indicate the proportion greatly exceeds that of the number of tumors diagnosed in these men. How many of these latent cancers are diagnosed depends largely on screening criteria. For example, setting a lower threshold for "positive" PSA tests and more intense biopsy techniques as follow-up could increase the yield of the latent cancers. In intensely screened young men, for whom follow-up by biopsies for a positive PSA test would likely be intense, the expected yield of the latent tumors is expected to be high.

(6) No other features, such as dose-response relationship or excess risk seen mostly in those with high exposures, raise suspicion.

In conclusion, there is no feature of the data that leads me to suspect that the apparent increase is nothing more than intense PSA screening in the Novartis male employees. Under such intense screening for men of this age, a large increase in the diagnosis of asymptomatic, organ-confined tumors would occur with almost certainty. The expected magnitude of such an increase cannot be known for certain, but this observed increase appears well within the realms of what would be expected with increased detection.

Please contact me if you have any questions.

Sincerely,

Edward Giovannucci, M.D., Sc.D.

EG:bv