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Report on Carcinogens
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ATTENTION: *Federal Register 69(97):* 28,940-28,944 (May 19, 2004). Call for Public Comments on 21 Substances, Mixtures and Exposure Circumstances Proposed for Listing in the Report on Carcinogens, Twelfth Edition.

SUMMARY: The comments below respond to a call for comments about atrazine (192-24-9), which the National Toxicology Program (NTP) proposed for listing in the twelfth Report on Carcinogens [*Federal Register 69(97):* 28,940-28,944 (May 19, 2004)], are provided by Daniel M. Byrd and James D. Wilson. We urge NTP not to list atrazine in the Report. Atrazine is neither a known human carcinogen, nor reasonably anticipated to be a human carcinogen. Thus, NTP should not list atrazine in the Twelfth Edition of the Report on Carcinogens. By listing atrazine based on misinterpretations, NTP will chill an important public health measure, employer-sponsored screening for cancers.

We understand the purpose of the Annual Report on Carcinogens as advising the public about exposures that increase the likelihood of their developing cancer. These listings should reflect the most reliable knowledge available to the scientific community. NTP will irremediably damage the value of the Annual Report, if the Report lists substances based on factually correct, but inappropriate and misleading, comparisons or on statistical increases in animal evidence, which require additional expert interpretation before the public can realize that exposure does not pose a serious risk.

(A) Human epidemiological data are available about atrazine. The human data about atrazine do not reveal human carcinogenic effects of atrazine.

(1) Recent human data about atrazine exposure arose from an occupational, prostatic cancer screening program.

An occupational study of 2045 workers at a manufacturing facility in St. Gabriel, LA between 1985 and 1997 (21,200 person-years, median 3.8 years worked) reported 46 observed

and 40 expected cases of all cancers combined [Standardized incidence ratio = 114, CIR = 83-152] (MacLennan et al., 2002). The study reported 11 workers with prostate cancer, when 6.3 cases were expected, which was not a statistically significant excess of cases (SIR = 175, CI = 87-312), with one comparison group. More cases of prostate cancer occurred among 757 actively working company employees (5/1.3, SIR = 394, CI = 128-920) than in 1288 contract employees (6/5.0, SIR = 119, CI = 44-260).

A recent U.S. Environmental Protection Agency (EPA) document reported data from a later study of the same facility, which found six additional cases with follow-up extended through 1999 (Delzell, 2001). In the later study, the St. Gabriel plant had accumulated 17 cases of prostate cancer. Fourteen of these 17 cases occurred among regular employees, most of whom participated in a prostate specific antigen (PSA) screening program. Twelve cases of prostate cancer occurred in company employees with atrazine exposure, compared with 4.7 to 6.7 expected, depending on the comparison populations, either overall LA rates or LA industrial corridor rates, for a significant excess of 5.3 to 7.3 cases.

In addition, interpretation of the St. Gabriel study as positive does not agree with the best quality epidemiological data about occupational exposure to atrazine and prostatic cancer, from the Agricultural Health Study (AHS). The AHS examined prostate cancer incidence in a prospective cohort study of 45 pesticides which involved 55,332 male pesticide applicators (Alavanja et al., 2003). Significant associations with prostate cancer incidence related to the use of methyl bromide and chlorinated pesticides by applicators more than 50 years old, but not to atrazine. In a nested case-control study, Hessel and coworkers (2004) found no evidence for an association between atrazine and prostate cancer.

(2) Appropriate comparisons are crucial to the interpretation of human data.

The St. Gabriel study did not generate an internal comparison group of unexposed workers similarly undergoing PSA screening. For interpretation, the NTP should rely on evidence of the effects of PSA screening on tumor detection from larger, more reliable studies. Thus, understanding the significance of the St. Gabriel data depends on the comparison group. If compared to unscreened workers, the incidence appears to increase. When compared to screened men unexposed to atrazine, the incidence of prostate cancer appears to decrease. The former comparison reveals more the effect of occupational screening. We do not advocate the interpretation of the latter comparison that exposure to atrazine as a prophyaxis against prostate cancer.

The NTP can exclude the possibility that atrazine exposure increases the risk of prostate tumors, based on the totality of epidemiological data; that is, the NTP needs to include negative associations between atrazine exposure and the incidence of cancers from studies which other, occasional studies suggest might be positive.

PSA screening at the St. Gabriel site provides a satisfactory alternative explanation for the

observed excess of tumor prevalence (MacLennan et al., 2002). In the published study, PSA screening led to detection of nine of eleven cases in company employees. In OPP's analysis, PSA screening led to the detection of ten of the twelve prostate cancer cases among company employees with exposure information. Staging of prostatic cancer cases also was consistent with a PSA screening hypothesis. Workers with prostate tumors were younger and had earlier stage, localized, asymptomatic tumors. The alternative interpretation, that atrazine caused the increase in cases of prostate cancer, requires a belief that PSA screening is ineffective.

(3) Other reports of human data are essentially negative.

In an ecological study, Mills (1998) found a positive correlation (0.67) between pounds of atrazine applied in each California county and prostate cancer among black persons in the same counties. Mills also observed similar, but negative, correlations for Hispanic, Asian or white persons. Because the study was ecological, and because the results for different subgroups diverged, the most likely explanation for the correlation between counties with more atrazine applied and counties with more prostate cancer among black persons, was random chance. Mills did not correct for simultaneous correlations. However, the study involved the intersection of four racial/ethnic/skin color groups, six diseases, and six pesticides, or 144 correlations. Of these, some would be expected to yield positive associations, based on random effects. No reason exists to expect a selective association with one racial group, contradicted by associations with other racial groups.

(4) Unconfirmed human surveys reveal conflicts between the site and kind of human cancer suspected, which include non-Hodgkins leukemias (NHL), female reproductive cancers (breast and ovarian cancers), and stomach cancers.

Farmers have shown increased rates of non-Hodgkin's lymphoma (NHL), but this association is not specific to atrazine exposure. A small, unconfirmed study of the t(14;18) translocation, a mutation often associated with non-Hodgkin's lymphoma (NHL), found positive relationships with several pesticides, including atrazine (OR 1.7, 95% CI = 1.0-2.8), suggesting a common factor, perhaps lifestyle, was involved (Schroeder et al., 2001). In an abstract, De Roos and coworkers (2003) reported that multiple pesticides were associated with increased incidence of non-Hodgkin's lymphoma among male farmers.

In an ecological study, Hopenhayn-Rich and coworkers (2002) suggested an association between atrazine exposure and the incidence of breast and ovarian cancers, based on an assumed mechanism. Their study involved indirect measures of atrazine exposure (public water measurements, acres of corn planted, and pounds of atrazine sold). However, their study produced negative results for atrazine and ovarian cancers and null results for atrazine and breast cancers. In another ecological survey in Ontario, Van Leeuwen and coworkers (1999) suggested that atrazine levels in drinking water positively associated with stomach cancer incidence and negatively associated with colon cancer incidence. These authors attributed the negative association to the nature of the study. However, their qualifications apply to all outcomes.

Further, other studies have not confirmed an association with stomach cancer, as this study does not confirm the associations noted in other studies, e.g., prostatic cancer and NHL.

Occasional, statistically positive results are intrinsic to the survey process in epidemiology. The important point about these surveys is that in the aggregate they do not confirm the positive results which crop up occasionally. Thus, oversight of all of the data is crucial to the interpretation of ecological studies and survey evidence. When accomplished, the net interpretation of the aggregate data is that atrazine exposure is has no human carcinogenic effects (Loosli, 1995; Sathiakumar and Delzell, 1997).

(B) The animal data about atrazine reveal an increased incidence in some rat strains, but these data do not suggest human carcinogenic effects.

(1) Tumor incidence increases in certain rat strains.

Atrazine reproducibly induces mammary tumors in female Sprague-Dawley rats (Stevens et al., 1994; Stevens et al., 1999). Similar kinds of observations have been reported from similar treatments in related strains (e.g., Long-Evans). However, similar treatment of female rats from strains not closely related to the Sprague-Dawley does not elicit such tumors, nor does similar treatment of mice. Furthermore, treatment of Sprague-Dawley rats with related chemicals, including methyl-s-triazines such as ametryn, prometryn and terbutryn, is not associated with an increase in mammary tumors (Hazelette and Green, 1987; Chau et al., 1991; Jessup, 1979; O'Conner et al., 1988). Neither is such treatment with a metabolite of atrazine, hydroxyatrazine (Chow and Emeigh-Hart, 1994). In addition, atrazine does not induce mammary tumors in unrelated rat strains or other species, such as mice. Thus, exposure to atrazine is associated with an increased rate of mammary tumors only in rats with a specific genetic background.

(2) Atrazine-induced mammary tumors in female rats related to the Sprague-Dawley strain are not predictive of a human response. Mode of action influences the interpretation of animal data.

Such questions are usually addressed by examining information about the mode of action of the substance under study. This information allows an inference about the biochemical process that leads to observed effect. Federal regulatory agencies regularly use mode-of action information to make regulatory decisions about chemical carcinogens, based on evaluation of the predictivity (or relevance) of animal tumor induction to human cancer risk.

Under EPA's proposed revision of its carcinogen risk assessment guideline [**61** *FR* 17960-18011 (April 23, 1996)], information about a substance's mode of action may be brought into the process when the evaluation relies on data from animal tests. Such information can inform two of the steps in the process: determination of the relevance of observations and choice of the algorithm for treatment of data from the critical study. In the first step, an assessor decides whether or not an observed increase in tumor prevalence relates to human risk. [Male Fisher rat

kidney tumors induced by *d*-limonene (EPA, 1991; Lehmann-McKeeman, 1995) and female Sprague-Dawley rat mammary tumors induced by atrazine are examples of animal tumors not relevant to human cancer risk.]

EPA's Office of Pesticide Programs (OPP) evaluated the mode of carcinogenic action of atrazine in Sprague-Dawley-related strains of female rats, including Long Evans and Wistar strains, which respond with the induction of mammary tumors (OPP, 2000, OPP, 2002). (Rat breeders earlier derived the outbred Long-Evans and Sprague-Dawley strains from Wistar stock. The three strains are related genetically.) The key step in the carcinogenic process involves disruption of estrous cycling in female rats of the responding strains. Atrazine disrupts estrous cycling by reducing the release of luteinizing hormone from the pituitary.

The primary lesion in the hypothalamus in female rats of the responding strains is not known but probably involves changes in the levels (or releases) of the brain catecholamine, dopamine, and it clearly involves decreased levels of gonadotropin-releasing hormone. Reduced gonadotropin releasing hormone migrating from the hypothalamus to the pituitary leads to reduced release of luteinizing hormone into the circulation. The disruption of estrous cycling in female rats of the responding rat strains consists of an extended diestrous period followed by a persistent estrous period. The disrupted state leads to higher than normal levels of endogenous estrogen and prolactin. Higher than normal levels of endogenous estrogen and prolactin induce the mammary tumors.

Strong evidence supports the idea that atrazine acts with low potency on CNS cells generating neurotransmitters (OPP, 2000b). Altered hypothalamic neurotransmitter and neuropeptide levels provide satisfactory explanations both for mammary and pituitary gland tumors in rats and for the sex and strain specificity of the tumor response in rats. Thus, experimental data support the conclusion that atrazine's mode of action involves the neuroendocrine system. A neuroendocrine-related mode of action also rationalizes the pituitary gland tumors seen in female rats of Sprague-Dawley and related strains.

In addition, it is generally observed that a response peculiar to some specific strain of rats has a very small probability of predicting a similar response in another species, e.g., in mice, let alone humans. Because the induction of mammary tumors by atrazine is peculiar to Sprague-Dawley rats, it is generally unlikely that atrazine would increase breast cancer incidence in humans. No reliable association has been reported between atrazine exposure and breast cancer rates in humans. Thus, atrazine cannot be concluded to be "reasonably anticipated to be a carcinogen" on the basis of the response in Sprague-Dawley rats.

If the neuroendocrine mode of action applied to male humans, the mode of action in female Sprague-Dawley rats would predict a *decrease* in prostate tumors, not an increase. Atrazine should cause a dose-dependent reduction in testosterone secretion by testicular Leydig cells, an effect observed in atrazine-treated male Sprague-Dawley rats (Trentacoste et al., 2001). Thus, the hypothesis that atrazine increases the risk of prostate cancer lacks biological

plausibility. Neuroendocrine disruption is not the likely cause of the prostatic tumors detected by PSA screening at the St. Gabriel plant, because neuroendocrine disruption predicts a decrease in the incidence of human male prostate tumors, not an increase.

(C) Labeling atrazine either as "a known human carcinogen" or "reasonably anticipated to be a human carcinogen," flying in the face of the most reliable science, will both harm NTP and chill employers' efforts to improve the health of their workers.

We urge NTP to adopt EPA's classification of atrazine as "Not Likely to Be Carcinogenic to Humans." OPP initially made this classification after a review of mammary and pituitary gland tumors observed in atrazine-treated female Sprague-Dawley rats. Atrazine-induced rat tumors are strain and sex specific. Atrazine does not induce mammary and pituitary gland tumors in mice, in male rats, or in female rats of several strains. The usual mode of chemical carcinogenesis is somatic cell mutation. However, negative mutagenicity studies contradict the idea that atrazine, or a metabolite of atrazine, forms DNA adducts or causes some other kind of mutagenic lesion, such as a chromosomal abnormality (OPP. 2000a). A somatic mutation mode of action also is difficult to reconcile with a highly specific sex, strain and species pattern of carcinogenesis. Subsequently, OPP staff reviewed the St. Gabriel data and found that this information was not dispositive of human carcinogenic effects.

EPA's Risk Characterization Policy calls for a transparent process and products that are clear, consistent and reasonable (EPA, 1995; SPC, 2000). The NTP's proposed listing does not advance a rationale to disagree with the following statement.

> "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."

Thus, no scientific basis exists to reclassify atrazine as a human carcinogen right now. Risk characterization needs procedures to cope with spurious events, particularly when the kind of study, such as an epidemiology study, because of the stochastic basis of its measurements and interpretation, is expected to generate spurious results on a regular basis. Better detection of tumors is one explanation for spurious increases. EPA currently attempts to find consistency and reasonableness in risk characterization of carcinogens is through the application of a modification of the Bradford Hill criteria (Byrd and Cothern, 2000). One of the Hill criteria is biological plausibility. However, the action of atrazine in Sprague-Dawley rats, if it applied to human carcinogenesis at all, should decrease the incidence of prostate tumors.

The clear purpose of the Annual Report on Carcinogens is one of providing the public

reliable, science-based information on possible threats to health. If the NTP warns about exposures for which the available scientific evidence does not support such a conclusion, it will further damage the credibility and usefulness of this report. Americans are already discounting warnings, as more and more examples of over-zealous warnings come to light. It behooves NTP to act judiciously and not misinterpret the data.

Labeling atrazine as a human carcinogen will directly harm public health by raising the cost to employers, or eliminating, the provision of health-screening services to their employers. The medical profession knows that increasing the rate of screening for a common condition in any subpopulation results in an increase in the apparent prevalence of that condition, unless the screen fails to detect. This truism is the obverse of the"healthy worker effect." Worker groups initially selected for good health, and provided with better access to medical care, generally exhibit lower rates of chronic conditions. Clearly, finding serious conditions early-on in a screen will increase the likelihood of a favorable outcome later. Obviously, effective screening benefits public health.

Yet, by misinterpreting observations made in screened occupational cohorts, and labeling a company's product, NTP imposes, not only a cost on that company, but inhibits all occupational screening. The lesson will not be lost on the American industrial sector in general. Thus NTP's unwarranted "listing" of atrazine would be inimical to public health. NTP should not take this action.

DISCLAIMER:

Both commentors have testified before EPA's OPP Scientific Advisory Panel, have submitted comments to OPP, and have published papers about atrazine (CTRAPS, 1999; CTRAPS, 2001; CTRAPS, 2003a; CTRAPS, 2003b; Wilson, 2000a; Wilson, 2000b; Wilson, 2000c; Wilson, 2001).

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