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Subject: Comments on Announcement 2003-34

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DATE: July 31, 2003
TO: Public Information and Records Integrity Branch (PIRIB)
Information Resources and Services Division (7502C)
Office of Pesticide Programs (OPP)
U.S. Environmental Protection Agency (EPA)
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DOCKET ID NUMBER: OPP-2003-0186

BY EMAIL TO: opp-docket@epa.gov

ACTION: Consultants in Toxicology, Risk Assessment and Product Safety (CTRAPS), a biomedical consulting firm, submits these postmeeting comments in response to a call for public comments about the characterization of atrazine cancer epidemiology data, which EPA announced in the Federal Register 68(104): 32488-32490 (May 30, 2003), as part of the notice of a meeting of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP). CTRAPS previously commented at FIFRA-FQPA SAP meeting about a preliminary risk assessment for atrazine (CTRAPS, 2000) and similarly commented to OPP about the same preliminary risk assessment (CTRAPS, 2001). In addition, James D. Wilson, Vice-President of CTRAPS, previously submitted comments to OPP about atrazine and published articles about EPA′s application of existing and proposed cancer guidelines to atrazine (Wilson, 2000a; Wilson, 2000b; Wilson, 2000c; Wilson, 2001). A CTRAPS consultant, Daniel M. Byrd, Ph.D., D.A.B.T., attended the July 17, 2003 SAP meeting, submitted written comments, and testified orally (CTRAPS, 2003).

SUMMARY: EPA's Science Advisory Panel (SAP) gave the Agency advice (identified below) that OPP should ignore, dismiss, and reject, because the advice comes from unscientific, contradictory, and absurd reasoning. The SAP behaved irresponsibly in proffering this advice. Instead, we agree with OPP′s characterization of the workplace epidemiological data for atrazine.

(1) The SAP advised OPP not to exclude the possibility that atrazine exposure increases the risk of prostate tumors, based on the observation that the tumor rate increased in a population of workers at an atrazine manufacturing plant, following institution of a prostate specific antigen (PSA) screening program among those workers.

A priori, institution of such a program is expected to increase the frequency of identified prostate tumors, simply because of the increased effectiveness of detecting such tumors. Thus, a simple increase in the observed rate, by itself, does not support an association between the chemical and prostate cancer, let alone a causal relationship. In brief, this advice is wrong and should be ignored.

We note that the members of the Panel were fully aware of the limitations of the epidemiological observations. During the meeting, some Panel members stated and none objected that the SAP should reject a dose-response or exposure-response analysis, because of the small number of cases.

During the meeting, some Panel members stated and none objected that

EPA should divide the cases of men with prostate tumors at an atrazine manufacturing plant in different ways, for example, to reflect the application of PSA screening to the workforce and potential time lag in tumor detection. Yet, as even members of the Panel noted, the number of cases is too small to do so. Obviously, EPA cannot selectively divide the cohort for some purposes of analysis, if such a division is not statistically valid for other purposes. Thus, OPP should reject and ignore the SAP's advice that the cohort be subdivided for analysis.

Instead, we agree with OPP that the available data do not support a relationship between atrazine exposure and human prostatic cancer. Atrazine is not likely to be the primary factor in the prostatic tumors observed in the St. Gabriel study, and a satisfactory alternative explanation exists for the observed excess tumor prevalence.

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 (SIR) = 114, CI = 83-152] (MacLennan et al., 2002). The study reported 11 workers with prostate cancer, when 6.3 were expected, also not a significant excess of cases (SIR = 175, CI = 87-312). However, 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).

OPP reports 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 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. However, this study did not have an available comparison population of workers similarly undergoing PSA screening. Instead, the SAP should rely on evidence of the effects of PSA screening on tumor detection from larger, more reliable studies.

The St. Gabriel study is not concordant 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.

An ecological study by Mills (1998) found a significant 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 negative correlations between pounds of atrazine applied in California counties and prostate cancer in the same counties for Hispanic, Asian or white persons. Because the study was ecological, and because the results for different subgroups diverge, the most likely explanation for the correlation between counties with more atrazine applied and counties with more prostate cancer among black persons, is random chance. Mills did not apply a correction factor for estimates of significance in correlation coefficients for the number of simultaneous

correlations. However, the study involved the intersection of four racial/ethnic/skin color groups, six diseases, and six pesticides, or 144 correlations.

OPP should ignore evidence presented to the SAP about studies to be published, unevaluated studies, and hearsay about possible effects in newer studies. Rumors are not reliable scientific information and should be dismissed.

The use of 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 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.

(2) This SAP review deviated significantly from the standards expected for any serious technical review of scientific data that relates to product safety. It appeared to us that the panel as a whole lacked the scientific knowledge and expertise to evaluate the data. In addition, the dynamics of the group were remarkable. No dissenting views were expressed, even when panel members made statements clearly at variance with the truth.

Some Panel members stated and none objected that atrazine induces aromatase, contrary to the results of well-conducted experiments in appropriate animals.

The Panel seemed confused about the evidence that high doses of atrazine administered to certain strains of rats affects the prostate gland. However, the direction of the change seen in these treated rats – decreased prostate weight – indicates that atrazine decreases androgenic stimulation. Under these conditions, the risk of developing prostate cancer should decrease. A decrease in gonadal stimulation by luteinizing hormone is consistent with extensive data about effects in both sexes of atrazine-treated Sprague-Dawley rats. Thus, the Panel had the direction of expected change wrong during its deliberations.

A neuroendocrine-related mode of action also explains the mammary and pituitary gland tumors seen in female rats of Sprague-Dawley and related strains. Neuroendocrine disruption is not the likely cause of the prostatic tumors observed in St. Gabriel, because this mode of action would predict a decrease in human male prostate tumors, not an increase.

OPP′s task, and the SAP′s advice, should relate to whether detection of persons with prostate tumors in excess of expectation is dispositive evidence of a human carcinogenic effect, not whether epidemiological evidence can reject the possibility that atrazine effects contributed to the excess. Scientifically, proof of a negative is extremely difficult, if not impossible. The SAP′s advice that an effect of atrazine could not be rejected, could be said of any epidemiological study, whether an increase, decrease, or no effect occurred.

Instead, we agree with OPP′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.

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. However, if it 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.

Atrazine reproducibly induces mammary tumors in female Sprague-Dawley rats (Stevens et al., 1994; Stevens et al., 1999). However, methyl-s-triazines, such as ametryn, prometryn and terbutryn, do not (Hazelette and Green, 1987; Chau et al., 1991; Jessup, 1979; O′Conner et al., 1988). A metabolite of atrazine, hydroxyatrazine, also does not induce mammary tumors in female Sprague-Dawley rats (Chow and Emeigh-Hart, 1994). In addition, atrazine does not induce mammary tumors in unrelated rat strains or other species, such as mice.

OPP has prepared two scientific evaluations of 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 closely related genetically.) According to OPP, and to other scientists, 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 lutenizing 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.

Mammary tissues of the female human also respond to elevated levels of estrogens with the induction of mammary tumors, although not to higher

levels of prolactin. Thus, understanding the relevance of the rat mammary tumors for human risk is an important task.

Scientists have repeatedly observed the induction of mammary tumors by atrazine in several Sprague-Dawley-related strains of rats, but not in other rat strains or in mice. The relevance of the rat mammary tumor induction for human risk translates into a scientific question of whether humans most resemble the responding rat strains or instead, the non-responding rat strains and mice.

(3) The panel displayed an inadequate knowledge of EPA′s authority and the regulatory process.

Some Panel members stated and none objected that EPA should conduct studies of atrazine manufacturing facilities in other countries owned by companies that are not registrants, which EPA obviously lacks authority to do.

Some Panel members stated and none objected that EPA had wrongly empaneled the group. Yet the meeting was a response to a lawsuit, not an entirely voluntary action on EPA′s part.

Some Panel members erroneously stated and none objected that EPA had never reviewed the epidemiology of atrazine comprehensively.

(4) We conclude that something went badly awry in the panel selection process.

When an entire group reaches bizarre scientific conclusions without dissent, something is wrong with the composition of the group. For the panel to reach conclusions about the interpretation of epidemiological data, based on, or strongly influenced by, theories of biological plausibility, the panel required expertise in endocrinology and toxicology. During the meeting, the absence of both skills was on display.

Dr. Handwerger accepted the possibility that atrazine induces prostate cancer and at the same time believe that high dose of atrazine reduce testosterone levels and decrease sperm count. Dr. Handwerger concluded that atrazine was an endocrine disruptor and suggested that it would decrease male fertility. Based on this rationale, he wanted more evidence about the fertility of the St. Gabriel men. Based on evidence in male Sprague-Dawley rats, atrazine might decrease human fertilty. However, the rat no-effect level was 50 mg/kg/day, whereas the exposure to atrazine in the plant ranged between 0.008 and 0.1 mg/kg/day.

Dr. Hopenhayen brought up Gillette′s aromatase data in alligators. Doing so reflected a failure to understand that up-regulation of aromatase, proposed by Hayes as a mechanism of feminization of male frogs, is not relevant to a discussion of prostate cancer in mammals. If anything, up-regulation of aromatase activity is at odds with studies of mammals administered atrazine.

Dr. Rief suggested that Syngenta retain DNA samples from the twelve cases in the hope that some time in the future, scientists might be able to use such DNA samples to understand why these individuals got prostate cancer. Scientifically, DNA typing would only prove useful in a future study, if DNA samples were obtained from all persons in the cohort. Practically, the authority of Syngenta or EPA to obtain DNA samples is dubious. In addition, Dr. Reif′s comment poses the hypothetical, future

development of a technology, which might be used to investigate an event (twelve cases of prostate cancer). Such genetic probing would not illuminate the question before the SAP. It would demand the discovery of some hypothetical "atrazine sensitivity gene," when the evidence clearly shows that a simpler, alternative explanation is responsible for the twelve cases: improved detection of tumors through PSA screening.

Dr. Knobeloch postulated, and apparently believed, that atrazine promotes tumors. No evidence supports the notion that atrazine promotes tumors initiated in other ways. Instead, an earlier SAP, which included members with more relevant qualifications, concluded that the mode of action underlying atrazine effects on mammary tumors in female Sprague-Dawley rats related to effects on the rat hypothalamic-pituitary axis. Dr. Knobeloch also suggested grouping together the moderately and highly exposed cases, when the highly exposed workers experienced a longer duration and higher exposure to atrazine than workers in the moderately and least exposed groups. If the SAP, or Dr. Knobeloch, desired a more precise exposure-response relationship, a better procedure would be construction of a model and fitting the model to the exposure and disease circumstances of individuals.

(5) We agree with OPP′s cancer classification. Atrazine should not be considered a human carcinogen for regulatory purposes. EPA′s Risk Characterization Policy calls for a transparent process and products that are clear, consistent and reasonable. The SAP did 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. EPA′s risk characterization policy calls for a transparent process which generates clear, consistent and reasonable work products (EPA, 1995; SPC, 2000). OPP′s documentation, the availability of these documents, and public communications have given transparency and clarity to the process.

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, no member of the SAP advanced a reason why current knowledge of the action of atrazine in Sprague-Dawley rats, if it applied to human carcinogenesis at all, would not decrease the incidence of prostate tumors. Arm-waving statements about a disputed activity of atrazine in frogs or "endocrine disruption" cannot support any change in incidence of tumors in an endocrine-regulated organ, in either direction, as

scientific evidence of cancer causation. Proceeding in this way is at odds with scientific reasoning, which requires posing of a hypothesis and weighing of evidence in relation to the hypothesis. The direction of change is highly relevant to the support of a hypothesis.

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DATE: December 15, 2003

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ANNOUNCEMENT: 2003-34 of August 29, 2003 (Executive Office of the President)

SUBJECT: Office of Management and Budget Draft Bulletin on Peer Review and Information Quality under Executive Order 12866 and supplemental information quality guidelines [FR Doc. 03–23367]

ACTION: Consultants in Toxicology, Risk Assessment and Product Safety (CTRAPS) is submitting comments on Announcement 2003-34 of August 29, 2003 by Office of Information and Regulatory Affairs (OIRA) in the Executive Office of the President.

SUMMARY: CTRAPS is a biomedical consulting firm, not a manufacturer of products. CTRAPS does advise manufacturers about product safety, particularly in matters involving Federal regulation. CTRAPS has commented extensively on scientific documents supporting regulations prepared by Federal Agencies and participated in peer reviews of the documents. Thus, CTRAPS is vitally interested in OIRA's proposal for a standardized process to subject significant regulatory support documents to peer review by qualified specialists. At a minimum, OIRA's Bulletin, when final, will impose a highly desirable, government-wide standard for peer review of draft documents which support regulations. In our opinion, peer reviews of draft documents supporting regulations have generally improved the quality of the documents and of the regulations based on these documents. However, peer review is not quite the panacea that OIRA imagines. OIRA can improve the draft Bulletin.

COMMENTS: OIRA's draft Bulletin seeks to implement a good idea: obligatory peer reviews of documents supporting Federal regulations. Consistently peer reviewing support documents will generally help Agencies discharge their rule making responsibilities more effectively. Government-wide peer reviews will help OMB increase the technical competence of rules and

obtain greater consistency across government. Peer review makes sense as a quality control measure as a part of general rule-making authority.

OIRA's draft Bulletin contains many meritorious components. For example, documentation of the peer review will help to achieve many of the apparent aims of government-wide peer review: better consistency and improved technical competence of regulatory support documents.

Planning and budgeting for peer reviews of support documents are potentially the most important aspects of the draft Bulletin. The typical Agency excuse not to obtain peer review of a regulatory support document involves a lack of funds and/or time. A requirement for Agency planning and budgeting will eliminate these excuses and force a step for peer review of support documents into the development of regulations. Further, documentation of the plans and budgets will permit OIRA to monitor the government-wide peer review process. OIRA can compare the duration of reviews and the actual expenditures for reviews with these plans to determine the costs of peer reviews better.

The draft Bulletin goes into legislative authority to require peer review in detail. However, OIRA need not get overly worried about its legislative authority. The draft Bulletin cites three sources of authority: (1) Section 515 of the Treasury and General Government Appropriations Act for Fiscal Year 2001 (P.L. 106-554; H.R. 5658), (2) 44 U.S.C. §§ 3504(d)(1), 3506(a)(1)(B), and (3) Executive Order 12866, as amended. However, the U.S. Government operates through a separation of powers under the Constitution. The President heads an independent Administrative Branch, and OMB carries out the President's mandate, consistent with the Constitution.

This view of the authority to require peer reviews of regulatory support documents does pose one problem. OMB is not an independent Agency, neither are the Departments reporting directly to the President. The authorizing legislation for the independent Federal Agencies will require review to insure that all of them fall under the President's administration.

OIRA has correctly specified the application of Federal Advisory Committee Act (FACA) in subsection 4(a) of the draft bulletin. Because of a bizarre ruling in *Byrd v. EPA*, Agencies working in the District of Columbia might try to avoid the application of FACA to peer reviews, by hiring a contractor to conduct the review [See U.S. Court of Appeals for the District of Columbia Circuit, Decision number 98-5180, 174 F.3d 239; 1999 U.S. App. (April 30, 1999)]. While Agencies should not be able to avoid FACA through the expedient of hiring a contractor, the Judge in *Byrd v. EPA*, Thomas Penfield Jackson, misunderstood the ruling in another case, *Food Chemical News v. FDA*, by Judge Ruth Bader Ginsburg.

Judge Jackson created a "contractor exemption," although only for the District of Columbia. FACA does not contain a contractor exemption. FACA interacts with peer review, but a meeting subject to FACA is not necessarily a peer review. OIRA and Federal Agencies should not exempt contractors from the reach of the Draft Bulletin. The proposed language in the draft Bulletin will accomplish this goal.

OIRA might replace the term, "scientific" with "technical," as a modifier of "peer review" throughout the draft Bulletin. Otherwise, OIRA will become engaged in arguments with about the meaning of "science." For example, the peer review process applied to journal publication is not like the peer review process essential to obtain minimum quality of regulatory support documents. The second process resembles and invokes existing Good Laboratory Practices regulations. Instead of publication in a peer-reviewed journal, OIRA probably means to apply scientific weight of the evidence to the data used in regulatory support documents. However, the application of weight of the evidence will create new problems in a final Bulletin. Peer review does not establish data as factual or reproducible. Peer review is not a good procedure to detect fraud.

"Science" usually means that an observation or inference meets four criteria: (1) adequacy of measurement, (2) control of conditions of the observation or experiment (elimination of potential explanations based on confounders), (3) reproducibility (which differs from weight of the evidence), and (4) availability. The last of these criteria, availability, often is the reason that stakeholders become concerned with peer review processes. The application of FACA to peer review processes can be the only opportunity for the public to obtain the data which concern an Agency in the development of a regulation. Data availability is a highly desirable element of an open regulatory process. However, it is not the same as peer review, which should not be made to bear this burden. In addition, peer review is broader than science. For example, it includes accounting practices.

OIRA can improve the draft Bulletin by making the development of regulations under the Administrative Procedures Act its focal point, not the distribution of documents under the Paperwork Reduction Act. If distribution of documents remains the principal concern of the draft Bulletin, OIRA will have to resolve a paradox. How does an Agency distribute a draft document to peer reviewers before it has been peer reviewed? Instead, if the peer review of documents supporting the development of a regulation is the subject of the final Bulletin, a support document would undergo external peer review before Agency use in developing a final regulation. The peer review would become a step in the process before promulgation of a final regulation. This approach also would eliminate problems about the availability of public comments to peer reviewers. An Agency would relay to its selected reviewers the comments submitted by stakeholders in response to an Agency's proposed regulation.

This suggested improvement would advance OMB's aim of improving the quality of documents supporting regulations and thus, governmental regulations on a systematic basis. Proposed regulations come under the informal rule making provisions of the Administrative Procedures Act. Creation of a support document is an early step in the development of a proposed rule, and falls under the administrative control of the President and of OMB. Requiring universal and uniform peer review of support documents before their use in proposed regulations will not generate a paradox. OMB can request peer reviews by Agencies as part of the application of the Administrative Procedures Act and to diminish reversals during judicial reviews.

OIRA can improve the specificity of language in the draft Bulletin. OIRA can clarify that Agencies can peer review activities exempted from the reach of the draft Bulletin, e.g., emergency rules and decisions. The requirements of the draft Bulletin should not create a bar or prohibition to peer review. OIRA can clarify that delegated decision-making by expert panels is not peer review. Peer review panels should be composed of disinterested experts, not stakeholders or representatives of stakeholders with specific interests in the outcome of a regulation.

OIRA may want to decrease the potential number of rule makings affected by the draft Bulletin by narrowing its application to more costly rules. The current language about "significant regulatory information" and "especially significant regulatory information" is confusing. CTRAPS also recommends that the final Bulletin cite two previous reports about peer reviews:

NEPI (National Environmental Policy Institute), *Enhancing the Quality of Science in the Regulatory Process.* Washington, DC (1998).

NEPI (National Environmental Policy Institute), *Enhancing the Integrity and Transparency of Science in the Regulatory Process.* Washington, DC (1996).

OIRA should consider peer reviewing the draft Bulletin to demonstrate the efficiency of peer review. The recent National Academy of Sciences (NAS) meeting on the draft Bulletin was a step forward in this regard [Science, Technology, and Law Program, Workshop on Peer Review of Regulatory Science and Technical Information, National Research Council, Washington, DC (November 18, 2003). The final Bulletin might cite more examples of peer reviews. The Environmental Protection Agency's (EPA's) assessment of noncancer risks of benzene is a good example of the advantages of peer review. During it, reviewers explained to EPA that the contractor-generated document was largely copied from an earlier Agency for Toxic Substances and Disease Registry toxicology profile.

Recent Federal Insecticide, Fungicide and Rodenticide Act Scientific Advisory Panel reviews also demonstrate some potential pitfalls. A peer review process can make an Agency more vulnerable to a takeover by an advocacy group. {See the appended postmeeting comments by Consultants in Toxicology, Risk Assessment and Product Safety about the characterization of atrazine cancer epidemiology data, submitted to the Office of Pesticide Programs of the U.S. Environmental Protection Agency in response to an announcement in the Federal Register 68(104): 32488-32490 (May 30, 2003). [Docket Identification Number: OPP-2003-0186] (July 31, 2003).} Similarly, during another recent review (of arsenic) an EPA scientist arranged to have former members of his graduate school department as panel members to review his work products. Although these individuals had no financial conflicts of interest, they could hardly be regarded as conflict free.

If OIRA chooses to evaluate the costs and benefits of peer review, OIRA will want to show more sensitivity to the potential costs of erroneous peer reviews. In any evaluation of peer

review costs, OIRA's options in relation to the timing of public comment for rule making will have major impacts. The choice between a peer review process that proceeds (1) in parallel with proposal of a rule, (2) before proposal, or (3) after proposal, will greatly influence costs. Peer review before (or as an early step in) rule making, likely will take little time and add little increment cost to a rule making. Other benefits of peer review, given a good attitude at practicing Agencies, include technically improved rules, less judicial reversal (not necessarily less going to court) of regulations, and explication of technical issues for future review. In the latter regard, OIRA's proposal of documentation of reviews will achieve benefits lost without documentation, as will appending the review and the Agency response to the review to the document.

Signed,

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Appended: Postmeeting comments by Consultants in Toxicology, Risk Assessment and Product Safety to the Office of Pesticide Programs, U.S. Environmental Protection Agency, about a review by the Federal Insecticide, Fungicide, and Rodenticide Act, Scientific Advisory Panel of the cancer characterization of atrazine [*Federal Register 68(104):* 32488-32490 (2003)] (July 31, 2003).