European Union Bans Atrazine, While the United States Negotiates Continued Use

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Atrazine is a common agricultural herbicide with endocrine disruptor activity. There is evidence that it interferes with reproduction and development, and may cause cancer. Although the U.S. Environmental Protection Agency (EPA) approved its continued use in October 2003, that same month the European Union (EU) announced a ban of atrazine because of ubiquitous and unpreventable water contamination. The authors reviewed regulatory procedures and government documents, and report efforts by the manufacturer of atrazine, Syngenta, to influence the U.S. atrazine assessment, by submitting flawed scientific data as evidence of no harm, and by meeting repeatedly and privately with EPA to negotiate the government's regulatory approach. Many of the details of these negotiations continue to be withheld from the public, despite EPA regulations and federal open-government laws that require such decisions to be made in the open. *Key words*: atrazine; legislation; industry influence; herbicide; regulation; ethics.

INT J OCCUP ENVIRON HEALTH 2006;12:260–267

About 1 billion pounds of pesticide are used annually in the United States, and about 30% of this is used on corn crops.[1] One of the most prevalent corn crop pesticides is atrazine, a broad-spectrum chlorotriazine herbicide; 85% of the 60–80 million pounds of atrazine used annually in the United States is on corn, with most of the rest used on sugarcane and sorghum crops. It is produced primarily by Syngenta Crop Protection, a Swiss-based company (formerly Novartis, and before that CibaGeigy). The worldwide production rate is approximately 70 million kg of active ingredient annually (154 million pounds).[2] Because of its high mobility and persistence in water (approximate half-life in aerobic soil is 146 days, in water 742 days), atrazine is the pesticide contaminant most frequently detected in U.S. waters.[1] Atrazine and its metabolites were detected in about 75% of stream samples and about 40% of ground-water samples in agricultural areas across the United States between 1992 and 2001, according to the most recent publicly available data in the 2006 U.S. Geological Survey (USGS) report.[1] Worldwide atrazine contamination in surface water has been reported to be as high as 50 parts per billion (ppb) in rivers and streams, 4,000 ppb in runoff from treated fields, and 2.5 ppb in rainfall in both high-use areas and areas far removed from original application sites.[2–4] The USGS reported atrazine contamination in streams in agricultural watersheds ranging from below the level of detection to as high as 201 ppb (mean = 0.07 ppb), over the period 1992–2001 (Table 1). The same report notes that the trends in atrazine use track fairly closely with trends in atrazine detections in agricultural waters; both have stayed fairly constant over the decade 1992–2001, with slight elevations in more recent years.[1]

CLOSED-DOOR NEGOTIATIONS

In November 2003 the Natural Resources Defense Council (NRDC) filed a lawsuit against EPA for failing to respond to a request for atrazine records under the Freedom of Information Act (FOIA).[5] As a result of that lawsuit and a subsequent FOIA request, NRDC has obtained thousands of pages of documents demonstrating that EPA repeatedly failed to comply with public-access provisions of the agency's pesticide-review regulations with respect to atrazine. Despite statutory requirements that agency advisory committees must be objective and publicly transparent,[6, 7]* EPA officials held approximately 50 private meetings with Syngenta regarding atrazine in 2003. EPA established and utilized two advisory committees composed only of representatives of Syngenta and EPA, without any public representation.[8] EPA's 2003 approval of atrazine relied on the final recommendations of these two committees, characterized by EPA as "joint efforts" between EPA and Syngenta to determine how atrazine should be regulated and where it should be monitored.[2] The first committee called itself the "Atrazine MOA [mode of action] Ecological Subgroup" (MOA Committee). According to the

Received from the Natural Resources Defense Council, Washington, D.C.

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In 1983, NRDC and others filed a lawsuit alleging that the pesticide industry was exerting improper, secret influence on EPA's decision-making in the pesticide registration process. In 1984, the parties entered into a Settlement Agreement that required EPA to develop regulations to open the registration process to public review and protect against undue industry influence.

TABLE 1 Atrazine Detections in U.S. Streams and Ground Water (1991–2001) Reported by the U.S. Geological Survey (USGS)

	Frequency of Detection (%)				Percentiles of Concentration (µg/L)				
	Total	>0.01 µg/L	>0.1 µg/L	>1 µg/L	25th	50th	75th	95th	Maximum
Streams at agricultural sites (n = 76), 1,852 samples	90.4	80.2	43	9.9	0.02	0.07	0.22	2.86	201*
Streams at undeveloped sites (*n* = 4), 59 samples	60.2	25.9	0	0	0	0	0.01	0.04	0.085
Ground water from agriculture land use wells (*n* = 1438)	41.9	29	13.6	1.5	ND	ND	0.02	0.36	4.78
Ground water from undeveloped land use wells (*n* = 67)	13.4	2.98	0	0	ND	ND	ND	0.01	0.018

These data are as reported by the U.S. Geological Survey on their public database. Information about pesticides in surface water can be accessed at: <http://ca.water.usgs.gov/pnsp/pestsw/Pest-SW_2001_Text.html> and information about pesticides in ground water can be accessed at: <http://ca.water.usgs.gov/pnsp/pestgw/Pest-GW_2001_Text.html>. ND = non detectable (below 0.007 µg/L). These public databases are expected to be updated within 2006.

*This value is an actual monitoring measurement; USGS notes that the precision of its analytical equipment is reduced at these high levels.

MOA Committee's Final Report, issued on October 22, 2003, the committee "was charged to reach agreement on the ecological level of concern (LOC), i.e., magnitude and duration of exposure of aquatic plants to atrazine that potentially adversely affect aquatic communities and/or ecosystems." The second committee called itself the "Atrazine Ecological Monitoring Program Subgroup" (Atrazine Monitoring Committee), with a membership composed solely of 17 individuals from either EPA or Syngenta and its consultants, including a legal defense firm (Latham and Watkins), and a product defense firm (Exponent, Inc.). According to this Committee's October 29, 2003, report, the committee "was charged with designing a monitoring program that could answer [several] management questions," including (a) in what water bodies are the triggers for atrazine effects being exceeded; (b) to what extent are they being exceeded; and (c) what mitigation is necessary to reduce those effects. While it is not unlawful for EPA to meet with outside parties, including pesticide registrants, it is unlawful for EPA to make decisions about re-registration or to commit to a course of action in meetings with only one party.

Although the committee identified 10,000 watersheds at risk, and more than 1,000 watersheds at highest risk, for atrazine contamination, EPA accepted the committee's recommendation that flowing water bodies be chosen from only 40 specific watersheds to conduct a monitoring program over a two year period.[2]

These private negotiations compromised ethical and scientific standards, and violated public trust in a federal agency charged with protection of human health and ecological integrity. As a federal judge ruled in an unrelated pesticide lawsuit, "EPA is not in the business of reaching consensus with the 'stakeholders' it regulates. EPA's job is independent review."[9]

REGULATORY HISTORY

Atrazine was first registered for use in the United States in 1958. By 1991, repeated detection of atrazine in the drinking water supply prompted EPA's Office of Water to set the limit for the annual average concentration in drinking water at 3 ppb—more permissive than the World Health Organization's international drinking water guidance of 2 ppb.[10] In 1994, EPA designated atrazine for additional regulatory scrutiny through a process called "Special Review," based on "concerns regarding the carcinogenic potential of atrazine and possible risks" from food and water.[2]

In contrast to the U.S. approach of allowing pollution to occur until there is scientific evidence of its risks, the European Union has a uniform limit of 0.1 ppb for the residue of any pesticide in drinking and ground water.[11] While scientists representing Syngenta characterize this standard as "neither health-based nor scientifically supported,"[12] it appears that the E.U. generally adopts the position that it is unhealthy to drink pesticide-contaminated water, arguably a health-based and scientifically-supported position. Based on the inability to keep water contamination below this level, European regulators announced a ban on atrazine use in October 2003,[13] one week before the U.S. EPA approved its continued use.[2]

OVERVIEW OF POTENTIAL HEALTH EFFECTS

There is some evidence that exposure to atrazine may be associated with cancers in humans (lung, bladder, non-Hodgkin's lymphoma, leukemia, multiple myeloma, ovarian cancer, colon cancer),[14, 15] cancer in laboratory rats (mammary, uterine, combined leukemia and lymphoma),[15,16] delayed reproductive

development in male and female laboratory rodents,[17–19] reduced sperm quality in rodents[20] and humans,[21] male hermaphroditism in amphibians,[22, 23] and impaired immune system function leading to increased susceptibility to infection in amphibians[24] and juvenile rodents.[25]

The disruptive effects of atrazine on endocrine activity has been suggested to occur via multiple mechanisms, including inhibition of androgen receptors in mammals,[26] disruption of the hypothalamic control of pituitary–ovarian function in mammals,[27] and alteration of corticosterone and thyroid hormones in amphibians,[28] and by induction of aromatase that results in an increased conversion of androgen to estrogen in human cell lines,[29,30] amphibians,[22,23] and potentially in reptiles.[31] In addition to the endocrine effects, there is some evidence that atrazine may induce non-Hodgkin's lymphoma (NHL) cancer through a cytogenic mechanism; one study reported an elevated risk of NHL associated with atrazine use only in cases with a particular chromosomal translocation (OR 1.7, 95% CI = 1.0–2.8).[32]

Studies that consider exposures to pesticides in isolation may artificially underestimate risks from exposures to toxic mixtures that commonly occur in the real world.[35,36] One assessment of multiple pesticide exposures among men with NHL has reported a suggested superadditive effect of atrazine in combination with the pesticides carbofuran, diazinon, and alachlor.[33] Similarly, the Hayes lab recently examined the effects of atrazine in pesticide mixtures on frog viability and metamorphosis, and reported increased mortality of tadpoles exposed to multiple pesticides at levels that were non-lethal when occurring individually (0.1 ppb).[34] Exposure to multiple pesticides simultaneously is routine for human and wildlife populations; the USGS reported that more than 90% of the time, watershed streams had detections of two or more pesticides or metabolites, and about 20% of the time they had detections of ten or more pesticide contaminants.[1]

ENDOCRINE DISRUPTION IN AMPHIBIANS REARED IN CONTAMINATED WATER

In work initiated under contract to Syngenta and published in 2002, University of California Professor Tyrone Hayes reported that male laboratory frogs (*Xenopus laevis*) reared in water with as little as 0.1 ppb atrazine displayed abnormal gonadal development consistent with feminization, including hermaphrodites (males with ovaries).[23] The Hayes laboratory subsequently reported comparable findings of feminization of male *Rana pipiens* frogs from the wild at sites with water contaminated by atrazine and other pesticides.[22,37] Hayes had terminated his contractual relationship with Syngenta (at that time, Novartis) in 2000, expressing concern that the final report of any data was contingent upon approval by Novartis, and that data reports may "not be finalized in a timely manner, let alone published."[38]

In 2002 a Canadian laboratory reported reduced testicular size, incomplete testicular development, and decreased germ cell numbers in male *Xenopus laevis* frogs after 48 hours in water contaminated with 21 ppb atrazine.[39] In females exposed during ovary differentiation, a significant decline in primary and secondary oogonia was observed.[40] That same year, Syngenta-funded researchers at a scientific meeting reported preliminary findings of male intersex cane toads (*Bufo marinus*) with female-typical skin coloration in sugarcane fields contaminated with agriculture chemicals including atrazine as high as 20 ppb, but no intersex frogs from non-agriculture sites free of atrazine.[41,42] Subsequent Syngenta-funded field studies reported abnormalities in wild frogs from Michigan agriculture areas with high atrazine use, but did not report an association with atrazine contamination.[43] In 2003, Syngenta-funded researchers reported that laboratory treatment of *Xenopus laevis* larvae throughout development resulted in an increase in intersex frogs at 25 ppb atrazine, but not at lower concentrations (1, 10 ppb).[44] An independent research group reported that in four species of frog tadpoles exposed during early development to three concentrations of atrazine-contaminated water (3, 30, 100 ppb) for 30 days, survival was lowest at the lower contamination levels, compared with the higher levels, for three of the four species, a counter-intuitive pattern that has been reported with endocrine disruptors.[45] Because reproductive development and hormonal regulation is highly conserved among vertebrates, these findings are relevant for wildlife and humans exposed to atrazine during sexual differentiation.

ENDOCRINE DISRUPTION IN TEST RODENTS

Even before evidence of hormone disruption activity had emerged in amphibians, EPA scientists and others had been reporting that atrazine disrupts the normal progression of sexual development in rats. Reported findings included: dose-dependent decreased estrogen-induced surges of circulating prolactin and luteinizing hormone levels[27]; prostatitis in offspring of dams treated during nursing[46]; delayed puberty in males[19] and females[47] treated with atrazine by gavage from weaning until puberty; decreased sperm number and motility in adults[20]; and reduced testosterone production by testicular cells of juvenile rats exposed prior to puberty.[48] The disruption of endocrine pathways is thought to be the cause of observed mammary tumors in one strain of female rats (Sprague-Dawley); while this mechanism may be strain-specific, it is likely to have implications for risks in other species.[15,49–51]

ENDOCRINE EFFECTS IN EXPOSED MEN

A multi-center case–control study of fertile men in U.S. agrarian areas reported a significant association between poor semen quality (reduced sperm concentration and motility) and urinary atrazine metabolite levels above the level of detection (0.1 μg/g creatinine), compared with men from urban centers (OR = 11.3, 95% CI = 1.3–98.9).[21,53] It is alarming that far higher urinary metabolite levels have been found in male farmers who self-applied atrazine, ranging from 0.16 to 5.0 μg/g creatinine[54] (95% CI = 0.33–1.3),[55] suggesting that farmers that apply pesticide themselves (not professionally trained applicators) may represent a population at increased risk of reduced sperm quality from pesticide exposures.

CANCER TRENDS FROM RODENT STUDIES

In 1991 and again in 1999 the International Agency for Research on Cancer (IARC) surveyed both animal studies and human epidemiology relevant to potential cancer risks from atrazine. While neither data set is definitive, the expert scientific committee determined that there was sufficient evidence in experimental animals that atrazine causes cancer.[15] Animal studies reviewed by IARC in 1999[15] included the following: a Novartis-sponsored study of male and female mice administered atrazine in their diet reported no treatment-related increase in tumor incidence[49]; a rat oral-feeding study (Fischer 344/LATI rats) reported a dose-dependent increase in uterine adenocarcinomas and combined leukemia and lymphoma in females, and increased benign mammary tumors in males at high dose[56]; several rat oral-feeding studies (Fischer 344 rats) co-authored by Novartis-sponsored researchers reported no significant overall carcinogenic effects, or cancer effects by a mechanism not relevant to humans[50,57]; a similar rat feeding study (Sprague-Dawley rats), also by Novartis-sponsored authors reported a statistically significant early onset of mammary gland tumors[49,57]; another study in the same strain of rats reported an increase in mammary gland fibroadenomas and adenocarcinomas in females, and increased testicular tumors in males[49,51]; a significant increase in lymphomas among male Swiss albino mice given atrazine intraperitoneally was reported after only one year of treatment.[58]

There is reason to be concerned that prenatal and early-life exposures to atrazine may predispose an organism to later-life cancer through disruption of hormone activity. EPA scientists reported that rats exposed prenatally to atrazine, followed by exposure to the carcinogen dimethylbenz[a]anthracene, experienced delayed mammary bud outgrowth followed by an increase in multiplicity and volume of tumors and increased organ pathology in exposed female offspring, compared with non-atrazine treated controls exposed to dimethylbenz[a]anthracene.[52] A similar phenomenon of increased risk associated with early-life exposure has been reported for the well-described cancers and reproductive abnormalities resulting from human prenatal exposure to diethylstilbestrol (DES).

CANCER TRENDS FROM AGRICULTURAL COMMUNITIES

In 2004 the National Institutes of Health Agriculture Health Study reported a nonsignificant elevated cancer incidence suggestive of trends for cancers of the lung and bladder, non-Hodgkin's lymphoma, and multiple myeloma among pesticide applicators in U.S. agriculture areas where corn crops predominate.[14] Although human studies linking atrazine with cancer are individually inconclusive, numerous well-designed studies cumulatively suggest increased relative risks for certain cancers. Multiple studies have reported a nonsignificant increased relative risks for NHL (1.2 to 3-fold above background), lung cancer, bladder cancer, prostate cancer, multiple myeloma, and ovarian cancer (Table 2).[14,16,59–65] This trend of elevated cancer risks across multiple independent studies warrants serious concern and further study.

DISCOUNTING EVIDENCE

In IARC's 1999 review of atrazine, a classification of "possibly carcinogenic to humans" (group 2B) was warranted, in our opinion. This would have been consistent with the IARC criteria described in the preamble for agents for which there is "inadequate evidence of carcinogenicity" in humans and "sufficient evidence" in experimental animals. However, IARC brushed aside the animal evidence and chose the weaker, less protective classification of "not classifiable as to its carcinogenicity to humans" (group 3), because it concluded that there was "strong evidence that the mechanism by which atrazine increases the incidence of mammary gland tumours in Sprague-Dawley rats is not relevant to humans."[15] In our opinion, IARC's choice of a weaker classification was not based on "strong evidence," but rather on a lack of key information plus a failure to consider alternative mechanisms that might also be relevant. This questionable classification in the face of incomplete mechanistic data, and which was aided by a well-financed campaign to seed the scientific literature with negative results, is a distressing example that shows why more rigor is needed when considering mechanistic data. One former IARC director warned that: "If tests show those hypotheses to be incorrect, or if they do not account adequately for the wide range of susceptibility in humans, serious consequences for public health may follow."[66]

TABLE 2 Case–control Studies of Cancer among Populations Exposed to Atrazine and Other Pesticides.

Reference	Subjects (Cases) in Analysis	Exposure Contrast	RR (95% CI)*	Comments
Non-Hodgkin's lymphoma				
Hoar et al. (1986),[61] Kansas	170 men, 948 controls	Ever exposed to triazines v. never worked on a farm	1.9 (0.4–8.0)	Adjusted for phenoxyacetic acids
Cantor et al. (1992),[65] Iowa–Minnesota	622 men, 1,245 controls	Ever personally handled triazines v. never worked on a farm	1.2 (0.9–1.8)	Adjusted for exposure to other pesticides
Zahm et al. (1993)[63] pooled analysis, U.S.	993 men, 2,918 controls	Ever used atrazine v. never worked on a farm	1.4 (1.1–1.8)	Adjusted for age and state
MacLennan et al. (2002),[60] Louisana	757 workers v. LA industrial corridor	Company employees at triazine manufacturing plant	3.0 (62–878)	Median duration of employment 10.6 yr
MacLennan et al. (2002),[60] Louisana	1,861 men , 184 women	Company and contract employees at triazine manufacturing plant	1.36 (28–398)	NHL cases were only among company employees; they were older and had worked longer than contract employees.
DeRoos et al. (2003),[33] pooled analysis, U.S.	650 men, 1,933 controls	exposed v. not exposed for each of 47 pesticides analyzed	1.6 (1.1–2.5)	Adjusted for exposure to other pesticides
Miligi et al. (2003),[82] multi-center case–control study, Italy	1,525 cases, 1,232 controls	Exposed cases v. population control	Men: 1.0 (0.5–2.3); women 2.0 (0.4–14.4)	
Rusiecki et al. (2004),[14] Iowa, North Carolina	36,513 licensed applicators, 17,430 controls	Ever used atrazine v. never used	1.6 (0.62–4.16)	Suggested trend. Prospective cohort study
Multiple myeloma				
Rusiecki et al. (2004),[14] Iowa, North Carolina	36,513 licensed applicators	Ever used atrazine v. never used	1.6 (0.37–7.01)	Suggested trend. Prospective cohort study
Ovarian cancer				
Donna et al. (1989),[64] Italy	65 women	Definite exposure to triazines v. no exposure	2.7 (90% CI 1.0–6.9)	Not adjusted for exposure to other herbicides

*Relative risk and 95% confidence interval (CI).
†Studies using pooled analyses are not new data, and include data presented here in previous studies. This table is not meant to be a comprehensive or detailed assessment of atrazine epidemiology, but rather a summary of selected case–control epidemiologic studies. Detailed evaluation of some of these studies, as well as other studies that are not case–control design, can be found in the IARC Monograph, Volume 73 (1999), and in the original articles.

EPA DATA REVIEW IS INCOMPLETE

The EPA convened two scientific advisory panels of outside experts in the summer of 2003; the first panel was to review atrazine's endocrine effects,[67] and the second to review potential cancer risks.[68] In each case EPA requested only a limited data review, thereby effectively preventing its outside experts from providing advice based on a comprehensive data review.

The endocrine advisory panel was limited to a review of frog studies, including a dozen conducted by Syngenta within the year preceding the review, only one of which had been published at the time.[69] The Syngenta-supported research team has subsequently published some of these data along with additional study results that routinely fail to find effects attributable to levels of atrazine commonly found in the environment.[43,44,70–77] Significant concerns were raised by EPA scientists regarding the questionable quality of the Syngenta submissions, including design flaws, insufficient statistical power, and high variability. The EPA scientists' assessment included the following comments: "poor water quality and overcrowding"; "estradiol treatment failed to skew sex ratios significantly in favor of females as expected"; "contaminated controls";"large proportion of the animals were not developing at a normal rate"; "coefficients of variation ranged as high as 10,628%."[69] Rodent studies were not included in the review. Not surprisingly given the limitations of the review and questionable quality of the data under review, the panel's final report supported the EPA conclusion that "it is not possible to ascertain the relationship, if any, of atrazine exposure to development effects in amphibians."[78] This head-in-the-sand assessment continues; EPA has not integrated the hormone-disruption activity of atrazine into its assessment, claiming that it is unable to evaluate the relevant data until pre-validated "appropriate screening and/or testing protocols" have been developed.[2]

The cancer advisory panel was limited to consideration of prostate cancer risks only. The panel expressed its frustration with EPA's unduly narrow charge, stating that it was "misleading" to review prostate cancer data but not data pertaining to other cancer risks.[68] The panel also disagreed with EPA for asserting that there is no link between prostate cancer and atrazine, reminding EPA that in an advisory report several years earlier, the panel had expressed concern that several studies on NHL had been discounted by EPA.[79] The earlier advisory panel had also encouraged EPA to consider "whether hormonal effects in childhood or adolescence may have an impact on cancer occurrence in later years,"[79] something EPA continues to avoid considering in its assessment.

Following pressure from the Natural Resources Defense Council (NRDC), EPA has since agreed to review cancer risks more comprehensively in 2006.[80] Meanwhile, EPA continues to allow atrazine use, and has classified atrazine as "not likely to cause cancer in humans," a misleading classification that is often cited by Syngenta and atrazine users.

DISCUSSION

There is suggestive evidence of increased incidences of non-Hodgkin's lymphoma, leukemia, and multiple myeloma in people exposed to atrazine, particularly in combination with other agriculture chemicals. Evidence that atrazine impairs hormonal activity in humans and wildlife suggests that exposures during early life or to people with illnesses may be particularly damaging. Importantly, co-exposures to atrazine and other pesticides commonly found in agriculture watersheds may be much more hazardous than single-chemical exposures.[33–35] Despite these data, atrazine continues to be classified by EPA as "not likely" to cause cancer, and EPA maintains that its hormone-disruption activity cannot be evaluated due to the lack of appropriately pre-validated tests. This head-in-the-sand approach is in stark contrast to the decision by the European Union in 2005 to issue a ban on atrazine use. In this commentary we have tried to provide a survey of relevant scientific data, and develop the regulatory context surrounding the U.S. federal assessment of these data. Although there may be disagreement as to whether or not the atrazine manufacturer succeeded in its attempts to weaken the regulation of its product, there can be no doubt that such attempts were made. Through at least 50 private meetings, the manufacturer enjoyed considerably more access to regulators and the regulatory decision-making process than was extended to environmental groups, impacted communities, water utilities, and others through the public process.

In the United States, data used to regulate pesticides are primarily derived from industry-sponsored studies. In some cases, the data reports are submitted by the manufacturers' lawyers, suggesting that the science has undergone legal review. We suggest that this practice places an unrealistic expectation on the manufacturer to generate and submit data that may be potentially damning of its product, and an unrealistic burden on government experts to review studies that may be biased by design and incompletely reported. Alternate models may provide more transparency and credibility, and should be considered. For example, toxicity testing for chemical registration could be sponsored by industry, but performed in independent or government testing laboratories, with results directly available to government risk assessors and publicly accessible, limited only as absolutely necessary for legitimate protection of confidential business information. Recognizing problems of corporate malfeasance in reporting of drug trial data, Drummond Rennie, deputy editor of *JAMA*, was recently reported by the *Washington Post* calling for

"A perfectly independent agency. . . ," to conduct drug trials, saying, "There will be two classes of trials—the believable ones and the non-believable ones."[81] The situation for industrial chemicals is no different.

The authors thank the reviewers for excellent comments. They gratefully acknowledge partial funding for this work from the Beldon Foundation. Both authors are employed by an environmental nonprofit organization with an interest in regulation of chemicals that is as health-protective as feasible, and with ongoing litigation against EPA regarding safe regulation of atrazine.

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