ATTACHMENT A

NRDC & World Wildlife Fund, *Comments on Atrazine Preliminary Ecological Fate and Effects Risk Assessment* (Nov. 26, 2001)

NRDC
THE EARTH'S BEST DEFENSE

NATURAL RESOURCES DEFENSE COUNCIL

November 26, 2001

Public Information and Records Integrity Branch (PIRIB),
Information Resources and Services Division (7502C),
Office of Pesticide Programs (OPP), Environmental Protection Agency,
1200 Pennsylvania Ave., NW., Washington, DC 20460

Docket OPP-34237A for atrazine

Atrazine Preliminary Ecological Fate and Effects Risk Assessment

Federal Register: September 26, 2001 (Volume 66, Number 187)[Page 49180-49182]

Submitted electronically to opp-docket@epa.gov

Dear Sir or Madam:

These comments are being submitted on behalf of the Natural Resources Defense Council and the World Wildlife Fund (WWF). NRDC uses law, science, and the support of more than 500,000 members nationwide to protect the planet's wildlife and wild places and to ensure a safe and healthy environment for all living things. NRDC has no direct or indirect financial or fiduciary interest in the manufacture or sale of the atrazine pesticide forming the subject of these comments, or any other pesticide or chemical. WWF is a non-profit organization with over 1.2 million members in the U.S. WWF is dedicated to using the best available scientific knowledge to preserve the diversity and abundance of life on Earth by conserving endangered spaces, safeguarding endangered species, and addressing global threats to the planet's web of life.

I. INTRODUCTION

In our comments on the Revised Preliminary Human Health Risk Assessment for atrazine, we urged EPA to take steps to cancel this dangerous pesticide. EPA itself proposed to ban its sale or use in 1996 unless States developed local management plans to mitigate its unreasonable effects on groundwater. 61 Fed. Reg. 33,259 (June 26, 1996). The Ecological Risk Assessment makes the case for cancellation far stronger, considering EPA's conclusion that

> widespread environmental exposure has serious implications when compared to ecotoxicological endpoints of concern. The preliminary ecological risk assessment indicated that risk quotients exceeded the levels of concern for chronic effects on mammals, birds, fish, aquatic invertebrates and non-target plants are possible at maximum and in some cases typical use rates. A refined risk assessment focusing on the aquatic environment and using the extensive exposure monitoring data as well as additional ecotoxicological data found in the open literature, resulted in concerns for adverse toxicological effects on freshwater and estuarine plants and their communities as well as indirect adverse effects on aquatic invertebrate and fish populations at monitored atrazine levels in surface waters.

Reregistration Eligibility Science Chapter for Atrazine, Environmental Fate and Effects Chapter, p. 1 (hereinafter "EFEC") (Jan. 26, 2001). Incredibly, these compelling data also fail to present a complete picture of atrazine's ecological effects; as discussed in detail below, EPA's assessment does not include recent evidence that atrazine is a potent endocrine disruptor in frogs.

In view of the severe adverse environmental consequences detailed below, and considering EPA's obligation under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) to regulate pesticides in order to prevent "unreasonable adverse effects on the environment," FIFRA § 3(c)(5), we seriously question whether atrazine can safely be reregistered when the Agency considers its eligibility. At a minimum, these findings indicate a real need for EPA to insist on use restrictions to mitigate atrazine's deleterious effects. Myriad opportunities exist to reduce atrazine use by adopting alternative farming practices or by simply using less atrazine (research shows that up to 50 percent less would be equally effective) than the label recommends.[i]

NRDC also urges EPA to reassess both the ecological and human health effects of atrazine in view of the new data discussed in section IV below. The conclusions we summarize are of such

significance that NRDC believes that EPA must: (1) reevaluate atrazine's effects on the endocrine systems of wildlife, and its derivative effects on ecosystems; and (2) reopen its human health assessment to consider the implications that these new data have on EPA's evaluation of atrazine's effects on people. These reassessments should be done promptly then be made available for public review and comment. Further, in reconsidering the human health assessment, EPA should – if it has not already – consider the relevance of its observation that "atrazine is known to increase the toxicity of organophosphate pesticides" (EFEC, p. 43).

II. BACKGROUND

Atrazine, Its Uses, and Its Animal Health Effects

Atrazine is a synthetic triazine herbicide produced by Syngenta (the successor-in-interest to Ciba-Geigy and Novartis Crop Protection). Although the use of atrazine is banned or restricted in several European countries, it is the most widely used herbicide in the U.S. EPA estimates that up to 85 million pounds of atrazine are produced in the U.S. annually, mainly for use in the Midwest on corn (EFEC, pp. 1-3). It is predominantly applied during crop pre- planting and pre-emergence, and is applied directly to the soil, so that levels are highest during spring rainfall, coinciding with the breeding season for most aquatic organisms.

Atrazine leaches easily into groundwater, and is a widespread aquatic pollutant. Atrazine is persistent (EFEC, p. 9). It appears from field dissipation studies that atrazine is more persistent in colder climate; half-life ranges from 13, 58, and 260 days in the field (EFEC, p. 45). It is transported via spray drift through the atmosphere, via runoff to water, and back to the ground in rainfall (EFEC, p. 9-10).

Atrazine is a serious public health concern. Substantial evidence links atrazine with breast and prostate cancer. Atrazine has been identified by a number of agencies as an endocrine disruptor - the UK's Environment Agency, the European Union, the Oslo and Paris Commission Convention for the Protection of the Marine Environment of the North-East Atlantic, and the State of Illinois[ii]. Even Syngenta has reported on atrazine's various endocrine disrupting effects in submissions to

EPA. One of atrazine's modes of action involves the hypothalamic-pituitary-gonadal (HPG) axis. This first mode of action was previously postulated to be the only mode of action in EPA's human health risk assessment. Another mode of action involves stimulation of aromatase activity, thereby increasing endogenous conversion of androgens to estrogens. This mode of action has been supported by work in fish, alligators, frogs, and human cells.[iii] [iv] [v] Recent work indicates that there may be no biologically-identifiable threshold for this latter mode of action. In fact, atrazine may disrupt hormonally-regulated development in amphibians at levels below ambient levels in many U.S. water bodies.[vi]

Key Findings of Ecological Assessment

Runoff into streams and rivers is a major source of atrazine contamination, and the EFED report states that measured levels in the Midwest states regularly exceed 20 ppb, and have been shown to peak over 100 ppb following typical atrazine applications (EFEC, p. 21-29). These high concentrations may last for days, especially in spring when multiple fields in a watershed are being treated (EFEC, p. 29). After storm runoff, EFED reports that agricultural streams have atrazine concentrations exceeding 500 ppb (EFEC, p. 25). These peaks in atrazine water levels are the rule, not the exception, resulting from typical to maximum use rates, and a single pulse may last several days to weeks (EFEC, p. 45). The EFED reports that half of Midwestern streams and rivers exceed 3 ppb (the Safe Drinking Water Act Maximum Contaminant Level) following atrazine applications (EFEC, p. 26).

The report presents some data indicating atrazine and its toxic metabolites are transported through the atmosphere, and can be detected in over one-third of air and rainfall samples, taken from both agricultural and urban areas, at levels as high as 1 ppb (µg/L) (EFEC, p.10, 69-71). Atrazine and its chloro-degradates are widely detected in rainfall, with observed levels of 0.2 to 0.9 µg/L in late spring and summer. USGS estimates that about 0.6% of applied atrazine ends up in rainfall (EFEC, p .47). Clearly, atrazine pollution is widespread, in water, in soil, and in air, and is not limited to areas of local use.

The direct effects of atrazine on nontarget aquatic plants indicate a high risk, such that routine peaks in atrazine levels above 20 ppb cause death of some aquatic flora, and complete loss of some plant species (EFEC, p. 60; Kettle et al, 1987[vii]). As EPA acknowledges, these direct effects of atrazine alone may devastate the aquatic community by reducing oxygen levels and nutrients in the water, thereby risking further loss of aquatic plants and animals. EFED states that a reduction in primary production of algae (EC50 = 1 ppb), reduction in invertebrate populations (EC50 = 10 ppb), and a reduction in phytoplankton production (EC50 = 20 ppb) are real-world risks following seasonal atrazine exposures. The crippling effects on fish populations follow loss of aquatic vegetation within weeks to months (EFEC, p. 21). Brook trout, among the most sensitive aquatic animal, has a chronic NOAEC value of 65 ppb, and fish populations are likely to suffer reductions due to food loss and habitat damage at 20 ppb[viii]. At current use rates, atrazine may threaten the complex integrity of aquatic communities; a pond whose community is limited to only the most hardy, atrazine-resistant species may be less able to provide for the waterfowl and mammals who depend on aquatic environments for food and reproduction.

EFED strongly and correctly rejected the registrant's reliance on Giddings et al, 2000, who concluded that aquatic communities can easily recover from atrazine contamination at 50 µg/L. These authors argue that biomass and primary productivity are the key markers of a healthy ecosystem, and say that sensitive species would be replaced with less sensitive species which perform the same ecological functions. This is short-sighted, simplistic, and underestimates risk substantially. EFED rightly agrees with Kettle et al, 1987, who maintain that at 20 µg/L, recovery is uncertain, species diversity is very important, and the combined effects of atrazine with other pesticides would lower the tolerance of the plants to atrazine toxicity, making the whole aquatic community more vulnerable. These authors found that a single application of 20 µg/L (ppb) of atrazine to a pond reduced vegetation 60% within several months, and by 90% within a year. Bluegill (a very hardy species) was reduced 96% in a year. Indirect community effects resulted from the impacts of atrazine

on aquatic vegetation (EFEC, p. 21). Accordingly, we applaud EFED for rejecting 50 μg/L as a NOAEC for community-based effects for atrazine (EFEC, p.11).

The EFED report states that mammalian and avian reproduction chronic levels of concern (LOC) are routinely exceeded for several use scenarios (EFEC, p. 64-66). Following maximum use rates on sugarcane, chronic LOC is exceeded for mammalian reproduction by as high as 90-fold (NOAEL is 50 ppm for adult body weight reduction, and 10 ppm for pup weight reduction), and 4-fold for avian species (NOAEL is 225 ppm for egg production). Typical use rates for sugarcane, corn, and sorghum all resulted in risk quotients which exceeded the LOC (Risk Quotient (RQ) = 1) for mammalian and avian reproduction (RQ = 26-62). These are extremely high RQ's, and clearly represent a hazard for wildlife populations.

III. EPA FAILS TO ANALYZE ECOLOGICAL SIGNIFICANCE OF ITS FINDINGS

A glaring omission in EPA's Atrazine Environmental Fate and Effects Chapter is its failure to provide a scientific framework for translating its findings about the multiple individual biological impacts of atrazine exposure into conclusions about the ecological significance of the risks posed by the chemical. That is to say, although EPA presents atrazine's effects on numerous biological endpoints standing alone (terrestrial plants, birds, etc.), the Agency does not attempt to express what these individual concerns mean at the level of ecosystems. In human health risk assessments, EPA addresses a single, well-studied organism, and there is general agreement that humans and their health are important. Unfortunately, it is not so easy for ecosystems, where it is often difficult to single out organisms of concern or assess impacts on fundamental ecological processes. Without such an analysis, it is impossible for EPA to carry out its statutory duty to assess unreasonable adverse effects on the environment responsibly.

In its Guidelines for Ecological Risk Assessment (USEPA, 1998), EPA provides three phases for ecological risk assessments – problem formulation, analysis, and risk characterization. None of these were undertaken here. To the contrary, EPA has merely compiled scientific information relevant to the issue at hand in isolation from the decision it will ultimately be required

to make on re-registering atrazine. The Agency does not frame a decision context for this information, articulate the decision to be made, or even describe potentially conflicting public values involved in interpreting the scientific data presented. Very fundamental questions such as: "What do we want to protect?" (which would articulate particularly important resources at issue) and "What do we mean by "protect"? (which would state specific goals for the structure and/or function of aquatic systems impacted by atrazine) are not even presented, let alone answered in this report, yet are key to interpreting EPA's atrazine data. The document thus falls far short of that necessary for Agency risk managers and decision makers who must ultimately develop robust ecological risk conclusions about atrazine and creates problems for commenters who must reach their own conclusions about the ecological significance of the biological impacts described.

In NRDC's view, the fact that risk quotients exceed EPA levels of concern for chronic effects on mammals, birds, and fish, as well as other organisms, for maximum and in some cases even typical atrazine use rates clearly suggests that the chemical is having adverse effects on the environment. This conclusion is further bolstered by the data we describe below regarding atrazine's dramatic effects on frog sexual development, which occur at even lower use rates and which were apparently not even considered by EPA in its ecological analysis. Thus, in the absence of any evidence that these effects do not combine to threaten whole ecosystems, we are left to conclude that atrazine does, in fact, cause unreasonable adverse effects on the environment.

IV. EPA MUST CONSIDER EVIDENCE OF ENDOCRINE DISRUPTION IN AMPHIBIANS

Recent work by Dr. Tyrone Hayes of the University of California at Berkeley, which has been presented at numerous scientific meetings, demonstrates with certainty that frogs (*Xenopus laevis*) exposed to atrazine in the water at concentrations ***below 1 ppb*** suffered abnormalities in gonadal development, including feminization and hermaphroditism, which would likely render male frogs sterile (data on reproduction rates are not yet available)[ix]. In addition, these same exposures resulted

in a reduction in the size of the laryngeal muscle in male frogs, an important muscle used for the mating call of the frog.

Severe reproductive effects like those observed by Dr. Hayes would be expected to reduce the reproductive fitness of male frogs, and thus result in population reductions. Most concerning, these impacts take place at exposure levels below most endpoints used by the EPA to indicate toxicity, such as larval growth, developmental rate, time to metamorphosis, size at metamorphosis, or mortality. Such crude endpoints are inadequate to detect atrazine effects at 1 ppb, and yet, exposure at this concentration may reduce reproductive ability and thereby affect population survival. At 1 ppb and higher, Dr. Hayes observed a reduction in laryngeal muscle size in 80% of exposed males, and gonadal abnormalities in 20% of exposed frogs (hermaphrodites, multiple testes). All effects reported by Dr. Hayes, in experiments replicated 36 times in over 10,000 frogs, occurred at ecologically relevant doses and exposure scenarios.

Dr. Hayes demonstrates that there is a defined window of vulnerability in the development of frog reproductive organs, so that only frogs exposed to atrazine before 2 months, that is, pre-metamorphosis, are affected. During this period of vulnerability, exposure to atrazine in the aquatic environment at levels below 1 ppb had adverse effects on gonadal development. Because frogs will predictably be within this window of vulnerability during the spring runoff when atrazine levels peak in waterways, there is a clear risk of widespread effects on amphibian populations that would be too subtle to be detected with conventional current monitoring techniques. Thus, atrazine does not need to be persistent in a water body to cause these dramatic effects. Single exposures during a critical time in the life cycle of frogs are of concern.

Significantly, the prediction of widespread, subtle, yet devastating effects on wild amphibians proved correct when U.C. Berkeley researchers collected frogs from the wild (*Rana pipins*), across the U.S., they found a very high prevalence of free-ranging frogs with gonadal abnormalities, consistent with the prior laboratory observations of atrazine exposure. Of the affected frogs, 100% were found in the Midwest, where the highest levels of atrazine, alachlor, and metolachlor are found in the water

(all endocrine disrupting pesticides in common use in the Midwest), and 0% were found in the West[x]. Thus, this phenomenon is clearly not an artifact of laboratory testing.

These data are especially worrisome for several reasons. First, the potential effects of atrazine exposure on amphibians cannot be overstated. Because atrazine is predominantly applied during crop pre- planting and pre-emergence, exposure will be highest during spring rainfall, coinciding with the breeding season for most aquatic organisms and amphibians. Further, many amphibians breed in temporary pools, irrigation ditches, flooded fields and streams, where atrazine levels are expected to be highest after runoff. Second, the reproductive effects observed in frogs indicates that there may be no clear threshold for the effects of atrazine on sexual differentiation in amphibians, making exposures at current environmental levels an imminent hazard to wildlife and to endangered species. Finally, although the EPA has only seriously considered one mode of action to explain the effects of atrazine – that of the hypothalamic-pituitary-gonadal pathway – Dr. Hayes's work strongly supports another mechanism – that atrazine stimulates the aromatase-mediated conversion of androgens to estrogens. The aromatase hypothesis is also supported by work in other animal species, such as carp, alligators, and even human cell lines. Because aromatase expression has been shown to be relevant to breast cancer risk, and aromatase-inhibitors are under investigation for the treatment of breast cancer the data supporting the aromatase-stimulation hypothesis must also force reconsideration of EPA's human health risk assessment.[xi] [xii] Likewise, this mechanism of action is consistent with reports of increased ovarian estrogen secretion and prolonged estrus in atrazine-exposed rats, and has been cited by Ciba-Geigy researchers as the explanation for early onset of mammary and pituitary tumors in rats[xiii].

V. OTHER OMISSIONS IN THE RISK ASSESSMENT

Metabolites and Degradation Byproducts, Which Are Toxic, Are Not Tracked and Measured

Aside from any direct carcinogenic actions of atrazine, there is evidence that the herbicide may interact with nitrate fertilizers in the environment to form a more potent carcinogen, *N*-nitrosoatrazine (NNAT). Weisenburger et al. found that NNAT is readily formed when atrazine is

combined with nitrite in acidic conditions in the soil or in the stomach.[xiv] The authors concluded that, given the frequent coexistence of atrazine with nitrate fertilizers in agriculturally contaminated water, the potential carcinogen NNAT may be a common exposure accompanying atrazine use. Therefore, NNAT formation could be an underlying mechanism in the initiation of atrazine-associated non-Hodgkin's lymphoma.

In 1993 Meisner et al. tested NNAT on human lymphocytes to assess its genotoxicity. When human lymphocytes were exposed to very low levels of NNAT (concentrations as low as 0.0001 micrograms/ml) chromosome damage was induced. The authors concluded that "the increased incidence of stomach cancer, leukemia and lymphoma in farmers, who have the greatest exposure to both nitrates and atrazine, raises concerns about the safety of water supplies that contain both of these contaminants".[xv]

Chlorinated atrazine metabolites act as endocrine-disrupting agents in aquatic amphibians[xvi], small mammals[xvii], and humans[xviii], causing abnormal reproductive organ development and cancers of the reproductive organs. The EFED risk assessment discusses briefly the toxicity of the degradates, compared to parent atrazine (EFEC, p. 41-42). The Assessment notes that toxicity data for the degradates is not available for birds, fish, aquatic invertebrates, terrestrial plants, and acute oral mammals. This is a very serious data gap, given that the degradates are long-lived, and available data indicates that they are more chronically and acutely toxic than the parent atrazine (EFEC, p. 42).

In view of these studies showing that NNAT can be formed from atrazine and nitrate fertilizers in the environment, that NNAT may be a mutagen and carcinogen, and that chlorinated atrazine metabolites also cause adverse effects on reproduction and development, EPA must include these chemicals in the risk assessment. Failure to include NNAT may seriously underestimate the risk from atrazine in the real world environment. Failure to address the serious data gaps relative to the chlorinated atrazines may also lead to serious errors underestimating the ecological risks of this chemical.

EPA Does Not Address Endangered Species Concerns

Although the risk assessment identifies numerous scenarios under which atrazine may jeopardize endangered species, the document does not discuss whether or how EPA has consulted with the Fish and Wildlife Service (FWS) regarding compliance with the Endangered Species Act (ESA). EPA in particular does not suggest that it will require label changes to restrict uses that can threaten endangered species. To the contrary, the assessment states that the "Agency is not imposing label modifications at this time through the RED" (EFEC, p. 73).

According to the risk assessment, atrazine exposure exceeds levels of concern for several types of terrestrial species: acute risks to endangered species of small mammals (EFEC, p. 6), chronic risks to mammals and birds generally, that is, not endangered species alone (EFEC, p. 7), and to endangered terrestrial plants (EFEC, p. 8). In addition, estimates of pond exposures indicate that atrazine use will exceed levels of concern for several classes of endangered aquatic species (EFEC, pp. 55-58). Finally, EFED notes that other adverse effects are possible, including habitat loss (EFEC, pp. 73-74).

Section 7 of the ESA requires each federal agency to "insure that any action authorized, funded, or carried out by [a federal] agency . . . is not likely to jeopardize the continued existence of any endangered species or result in the destruction or adverse modification of habitat of such species which is determined by the Secretary . . . to be critical. . . ." 16 U.S.C. § 1536(a)(2). Governing regulations define federal "actions" subject to the Section 7 requirements as including "all activities or programs of any kind authorized, funded, or carried out, in whole or in part, by Federal agencies in the United States or upon the high seas." 50 C.F.R. § 402.02. Accordingly, "EPA in registering pesticides must ensure that its actions do not harm listed species." 54 Fed. Reg. 27,983, 27,984 (July 3, 1989).

Section 7(a)(2) of the ESA also requires that each agency make a determination regarding its impact on species "in consultation with and with the assistance of the Secretary." 16 U.S.C. § 1536(a)(2). The consultation referred to in Section 7(a)(2) requires each agency contemplating an action likely to affect a listed species to confer before taking the action.

In light of the Agency's risk findings and the legal requirements of the ESA, we request that you inform us immediately whether you have made any determination about whether the continued registration of atrazine will have any impact on endangered species, describe in detail any consultation you have conducted (or plan to conduct), and describe any actions that you are taking (or plan to take) to prevent any adverse impact that reregistration will have.

Monitoring Data May Not Detect Peaks

Although water monitoring programs routinely detect atrazine levels above 20 ppb, these data likely underestimate actual levels substantially. Water monitoring sample sites are not necessarily correlated with atrazine use sites, and in particular, may miss sites where multiple fields are treated with atrazine resulting in pooled runoff into a common water source. Levels of atrazine under these conditions are likely to be many times higher than single field sites[xix]. Similarly, data collection is not timed to correspond with worst-case scenarios, such as closely following atrazine applications, or following large storm runoff events, and thus most often misses these highly toxic environmental exposures (EFEC, p. 34, 44). Indeed, very high concentrations are not uncommon, reaching levels exceeding 500 ppm after storm runoff (EFEC, p. 25), and often greater than 100 ppm after atrazine application (EFEC, p. 24-25, 29).

CONCLUSION

In summary, NRDC is extremely concerned about the serious and widespread nature of the likely ecological risks of atrazine. EPA's own calculations indicate that current ecological levels are likely to pose a significant risk to numerous species under common use conditions. Yet EPA's calculations fail to take into account numerous factors, including sound scientific evidence, that must be included in an ecological risk assessment for atrazine. These serious omissions mean that the Agency is likely to be underestimating the environmental impact that the use of this pesticide is posing today. There is some urgency to resolve these issues, because the spring breeding season and major runoff season for atrazine is coming up in less than six months.

In follow-up to the ecological risk assessment of atrazine, NRDC makes the five following requests to EPA:

1) That EPA clarify that atrazine's mode of action includes not only effects on the hypothalamic-pituitary-gonadal axis, but also a stimulatory effect on aromatase in numerous species. This mode of action must be included in both the ecological and the human health risk assessments.

2) That EPA review and include, in the ecological risk assessment, the data submitted by Dr. Tyrone Hayes of U.C. Berkeley on the low-level effect of atrazine on amphibians.

3) That EPA immediately inform NRDC about the Agency's consultation with the Fish and Wildlife Service and efforts to address the effects of atrazine on endangered species.

4) That EPA include risk calculations for N-nitrosoatrazine and chlorinated atrazine metabolites in its ecological risk assessment; or alternatively, if quantification is not possible, that EPA gather the relevant data on this issue promptly and include an additional uncertainty factor in the risk calculations to account for the toxicity of the metabolites.

5) That EPA take prompt action to mitigate the risks to wildlife and the environment from atrazine prior to the upcoming spring runoff season.

Respectfully submitted,

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[i] See, e.g., Iowa State University, Pest Management In Iowa: Planning for the Future, at 67 (June 1996).

[ii] See http://www.nihs.go.jp/hse/environ/illiepatable.htm .

[iii] Sanderson JT, Letcher RJ, Heneweer M, Giesy JP, van Den Berg M. Effects of chloro-s-triazine herbicides and metabolites on aromatase activity in various human cell lines and on vitellogenin production in male carp hepatocytes. Environ Health Perspect. 2001 Oct;109(10):1027-31.

[iv] Sanderson JT, Seinen W, Giesy JP, van den Berg M. 2-Chloro-s-triazine herbicides induce aromatase (CYP19) activity in H295R human adrenocortical carcinoma cells: a novel mechanism for estrogenicity? Toxicol Sci. 2000 Mar;54(1):121-7.

[v] Crain DA, Guillette LJ Jr, Rooney AA, Pickford DB. Alterations in steroidogenesis in alligators (Alligator mississippiensis) exposed naturally and experimentally to environmental contaminants. Environ Health Perspect. 1997 May;105(5):528-33.

[vi] Hayes T. presentation at SETAC scientific meeting, Baltimore, Nov 14, 2001.

vii Kettle WD, deNoyelles F Jr, Heacock BD, Kadoum AM. Diet and reproductive success of bluegill recovered from experimental ponds treated with atrazine. Bull Environ Contam Toxicol 1987 Jan;38(1):47-52. MRID 45202912

viii Kettle et al, ibid.

ix Hayes T, Stuart A, Vonk A, Liu R. 2001. Atrazine disrupts sex differentiation in the African Clawed Frog (Xenopus laevis) at ecologically relevant doses. presentation at SETAC (Society of Environmental Toxicology and Chemistry) meeting, Baltimore, Nov. 14, 2001. Available online at http://abstracts.allenpress.com/setac-cgi/document.cgi?YEAR=2001&ID=34881

x Hayes T. presentation at SETAC scientific meeting, Baltimore, Nov 14, 2001.

[xi] Brueggemeier RW. Aromatase, aromatase inhibitors, and breast cancer. Am J Ther. 2001 Sep-Oct;8(5):333-44. Review.

[xii] Sasano H, Ozaki M. Aromatase expression and its localization in human breast cancer. J Steroid Biochem Mol Biol. 1997 Apr;61(3-6):293-8.

xiii Wetzel LT, Luempert LG 3rd, Breckenridge CB, Tisdel MO, Stevens JT, Thakur AK, Extrom PJ, Eldridge JC. 1994. Chronic effects of atrazine on estrus and mammary tumor formation in female Sprague-Dawley and Fischer 344 rats. J Toxicol Environ Health, 43 : 169-182

Eldridge JC, Fleenor-Heyser DG, Extrom PC, Wetzel LT, Breckenridge CB, Gillis JH, Luempert LG 3rd, Stevens JG. 1994. Short-term effects of chlorotriazines on estrus in female Sprague-Dawley and Fischer 344 rats. J Toxicol Environ Health, 43: 155-167

Eldridge JC,Wetzel LT, Tyrey L. 1999. Estrous cycle patterns of Sprague-Dawley rats during acute and chronic atrazine administration. Reprod Toxicol, 13(6): 491-499.

xiv Weisenburger DD, Joshi SS, Hickman TI, Babcock DM, Walker BA, Mirvish SS. N-nitrosoatrazine (NNAT) synthesis, chemical properties, acute toxicity, and mutagenicity. Proc Am Assoc Cancer Res 1987;28:103.

xv Meisner LF, Roloff BD, Belluck DA. In vitro effects of N-nitrosoatrazine on chromosome breakage. Arch Environ Contam and Toxicol 1993;24:108-12.

xvi Hayes et. al, op. cit.

xvii Stoker et. al, and Cooper et. al, op. cit.

xviii Update of the mortality among employees at the St. Gabriel, Louisana plant, op. cit.

xix Wauchope, 1978 found bulk field runoff had atrazine levels as high as 4,000 ppb