To Whom It May Concern,

I am writing to inform you that the US EPA has made their safety determinations regarding the herbicide atrazine based irrelevant and negative rodent data intentionally generated by Syngenta scientists to flood the literature so that the 'weight of evidence' detracts from the real and human health-relevant effects of atrazine- LIKELY that atrazine directly induces the estrogenic enzyme aromatase (CYP191A1) in the ovarian tissue of Sprague-Dawley (SD) rats to promote mammary carcinogenesis. The mechanisms by which atrazine induces aromatase (cAMP/PKA induction) in the SD rat ovary are conserved in the female post-menopausal breast and adipose tissue, and NO LEVEL of atrazine should be considered safe until simple laboratory tests performed by INDEPENDENT researchers prove otherwise. Seminal studies conducted by Syngenta scientists from 1991-1999 clearly demonstrated that atrazine promoted mammary tumor (MT) formation in SD rats by some mechanism that was DEPENDENT on excessive ovarian estrogen production. In the 20 years since, Syngenta scientists have conducted all their 'mechanistic studies' to demonstrate relevance to humans in OVARIECTOMIZED rats, or rats/mice in which MT formation is NOT promoted by estrogen. This is tantamount to studying type I diabetes in animals with no pancreas, or animals in which insulin does not regulate blood glucose levels at all. THIS IS ABSURD.

Syngenta is well-aware that they have flooded the literature with quasi-plausible mechanisms of action they can claim are 'irrelevant' to human health (LH surge). As you well know, present-day Syngenta is a product of a spin-off of inbred/epigenetically more similar strains. Other strains/models Syngenta deploys to generate negative data will in the human population than simply to divide NOELs by an 'uncertainty factor' of 1000 using only refractory and lot more sense to include a susceptible and outbred rodent model among different species tested to account for variation cast the SD rat aside as a 'uniquely susceptible species' when toxicology/carcinogenicity results are positive. It makes a negative. You cannot claim findings in the SD rat are only relevant to human health when the results are negative and model organism for dozens of chemicals over the decades, especially when toxicology/carcinogenicity results are

FALSEHOOD/Red Herring #1: Atrazine does not promote mammary carcinogenesis in the SD rat but only promotes EARLIER ONSET of MTs in a 'uniquely susceptible' species above the MTD:

Syngenta scientists conducting seminal studies in which atrazine was demonstrated to induce MTs in female ovary-intact SD rats CLEARLY understood that the ovary was the parenchymal tissue of estrogen production in this species and that excessive estrogen exposure induced by atrazine promoted mammary carcinogenesis (as it does in humans) in the SD rat. They later claimed that atrazine only promoted 'earlier onset' of MTs in the SD rat, which as a species has a high incidence of spontaneous MT formation in old age. However, regarding susceptibility, the very same can said of humans: if you live long enough, you may not die OF breast cancer, but you will likely die WITH breast cancer; so the SD rat should not be cast-aside as an 'unusually sensitive species'. Further, if we extrapolate this claim to humans, it means that rather than being diagnosed with breast cancer at 70, atrazine may cause you to be diagnosed with breast cancer at 35 years of age. The 'earlier onset' of MT formation line is ludicrous, and the EPA has defended the SD rat as a model organism for dozens of chemicals over the decades, especially when toxicology/carcinogenicity results are negative. You cannot claim findings in the SD rat are only relevant to human health when the results are negative and cast the SD rat aside as a 'uniquely susceptible species' when toxicology/carcinogenicity results are positive. It makes a lot more sense to include a susceptible and outbred rodent model among different species tested to account for variation in the human population than simply to divide NOELs by an 'uncertainty factor' of 1000 using only refractory and inbred/epigenetically more similar strains. Other strains/models Syngenta deploys to generate negative data will never develop MTs when exposed to atrazine because they are either incapable of producing ovarian estrogen (ovariectomized models, male rats) or unlike humans, develop MTs not promoted by estrogen (Fisher 344 rat, mice). Additionally, in seminal and follow-up studies, Syngenta scientists have exposed rats to doses of atrazine near or above the maximum tolerated dose (MTD, dose just short of inducing extreme weight loss that precedes premature death). All sex hormones of the HPG axis are controlled by negative feedback, and many hazards like atrazine are detoxified by enzymes that may be induced only above a certain threshold; for these reasons, it is conceivable lower, more biologically relevant levels of atrazine may be more harmful than higher doses frequently deployed by Syngenta scientists. This has been born out in numerous studies in many different species (PMID: 21419222).

FALSEHOOD/Red Herring #2: Atrazine crosses the blood-brain barrier to suppress LH pulsatility and induce 'reproductive senescence' in the SD rat, which itself secondarily promotes MT formation.
As previously stated, in seminal studies conducted in ovary-intact SD rats, it was clear that MT promotion by atrazine was DEPENDENT on enhancement of ovarian estradiol production by atrazine (PMID: 9972921, Table 6 compares ovariectomized vs intact SD rat MT incidence). WHY ON EARTH then, in the 20 years since, has the EPA accepted all the ‘mechanistic studies’ conducted by Syngenta scientists IN WHICH ALL THE RATS ARE OVA RIECTOMIZED? MT formation in the SD rat increases with lifetime estrogen exposure, as it does in humans; the tissue responsible for mammary carcinogenesis in the SD rat IS THE OVARY, where atrazine likely DIRECTLY, without need of influence from the hypothalamus or pituitary, induces the estrogen-producing enzyme aromatase by the same cAMP/PKA-mediated mechanisms as does LH (luteinizing hormone) from the pituitary (PMID: 12127262).

As the Fed EPA well knows, atrazine inhibits phosphodiesterases, which can lead to an increase in cAMP/cGMP - the tissue responsible for mammary carcinogenesis in the SD rat. In the 20 years since these seminal studies in SD rats have Syngenta scientists conducted “mechanistic studies” in totally irrelevant models, namely (1) Fisher 344 rats (not susceptible to MT formation) (2) ovariectomized rats (also not susceptible to MT formation)? How can this be allowed? IN OVA RIECTOMIZED (irrelevant) RATS, they claim that atrazine suppresses LH to induce premature ‘reproductive senescence.’ In the SD rat, contrary to human menopause, ‘reproductive senescence’ leads to increased ovarian estrogen production in old age (persistent estrus), and Syngenta scientists argue estrogen exposure secondary to atrazine-induced LH-suppression and ‘reproductive senescence’ promotes mammary carcinogenesis in the rat. Preposterously, they extrapolate these findings to humans, NOT on the basis of how atrazine affects estrogen, but on the basis that women experience different hormonal profiles in reproductive senescence than do RATS, to wit:

- atrazine induces MTs in aging female SD rats by suppressing the luteinizing hormone surge, thereby supporting a state of persistent estrus and prolonged exposure to endogenous estrogen and prolactin. This endocrine mode of action has low biological plausibility for women because women who undergo reproductive senescence have low rather than elevated levels of estrogen and prolactin. (PMID: 21768606)

THREE THINGS: (1) are Syngenta scientists really claiming atrazine is of low risk to women because if it may hasten onset of menopause and lower estrogen levels? (2) how can Syngenta scientists know if atrazine only increases ovarian estradiol production in the SD rat secondary to LH if they have only tested ovariectomized SD rats and never assessed the DIRECT affects of reasonable doses of atrazine on aromatase/estrogen production in SD rat ovarian cells in culture? (3) male-pattern behaviors including aggressiveness and sexuality are hard-wired in a narrow developmental window in utero by aromatase expression in the fetal brain (PMID: 19804754). Are Syngenta scientists really claiming atrazine can cross the blood-brain-barrier to affect brain sex hormones? How will the Corn Belt feel about that?

FALSEHOOD/Red Herring #3: Mechanisms of rat ovarian aromatase/estrogen induction by atrazine are irrelevant to humans. Lifetime estrogen exposure promotes breast/MT formation in women and in SD rats, and both suffer the disease disproportionately in old age; making the latter a defensible model organism to study breast tumorigenesis. The majority of cases in the US are diagnosed in post-menopausal women, when their ovaries are quiescent. However, aromatase expressed in the breast and adipose tissue of post-menopausal cases often becomes deregulated and with age can be expressed from ovary-specific gene promoters typically regulated by cAMP/PKA (protein kinase A) downstream of LH. Because atrazine inhibits phosphodiesterases to increase levels of cAMP/cGMP in cells (PMID: 12127262, PMID: 23022511, PMID: 15475179) it is plausible that the same mechanisms by which atrazine DIRECTLY induced aromatase in the rat ovary (cAMP/cGMP/PKA) may be operative in human postmenopausal breast and adipose tissue (cAMP/cGMP/PKA), leading to local elevations in estrogen that could fuel breast tumor formation. For these reasons, the effects of atrazine on aromatase expression should be tested in: (a) SD rat ovarian cells; (b) human breast epithelial and cancer cells (c) human breast pre-adipocytes, adipocytes, and fibroblasts (c) human breast tumor-proximal adipose fibroblasts (d) human pre-adipocytes and adipocytes derived from other depots in post-menopausal women.

You have based your MADLs on false hypotheses Syngenta has flooded the literature with to detract from probable human health-relevant mechanisms of atrazine action. YOU MUST reject/forestall Prop 65 MADLs based on these misleading and deceptive hypotheses until more biologically plausible mechanisms are ruled out. I have written the LA Physicians for Social Responsibility to petition for a public hearing.

Sincerely,
Theresa Ryan Stueve, Ph.D in Molecular Toxicology

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References by PMID (Pubmed ID):


