Atrazine and Human Health

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Abstract The atrazine, simazine, ametryne, propazine, its metabolites and its residues have been detected in surface water, rainwater, tile drainage, and groundwater at concentrations exceeding the maximum contaminant level of 3 mg/L set by the U.S. Environmental Protection Agency. Atrazine has a lot of adverse effect on health such as tumors, breast, ovarian, and uterine cancers as well as leukemia and lymphoma. It is an endocrine disrupting chemical interrupting regular hormone function and causing birth defects, reproductive tumors, and weight loss in amphibians as well as humans. It also causes induction of the detoxifying hepatic microsomal oxidative enzymes, continual synthesis of esterases, physiological adaptation to decreased esterase levels, and adaptation of cholinergic receptors. The main objective of the present work is to study the various effect of atrazine on human health.

Keywords Atrazine, Bioaccumulation, Health Effects, Metabolic Pathways, Microbial Degradation

1. Introduction

Atrazine is a chlorotriazine and consists of a ring structure, called the triazine ring, along with five nitrogen atoms and a chlorine atom. Pure atrazine is an odorless, white powder, not very volatile, reactive, or flammable. It is available in emulsifiable concentrate, wettable powder, granular and ready to use formulations. It gives off irritating or toxic fumes(or gases) in a fire. It can be absorbed into the body by ingestion. It decomposes on heating producing toxic fumes including hydrogen chloride, nitrogen oxides[1].

Atrazine is a herbicide and inhibits the photosynthesis in the target plants. It is water-soluble and can be transported in dissolved form[2]. It has been detected consistently in water bodies[3]. It is quite susceptible to leaching and/or runoff. Atrazine has also been reported in precipitation, so it can lead to contamination of pristine water resources. Approximately 1 to 6% of the applied herbicides is released to the aquatic environment. Aged and persistent herbicides can become recalcitrant due to increased sorption and decreased bioavailability over time[4].

This does enter the environment under normal use through run off, from manufacture, formulation, transport, and disposal. Persistence of atrazine in the soil is critical and has been shown to vary from 8 days to up to 60 days[5].

Due to its endocrine disruptor effects, possible carcinogenic effect, and epidemiological connection to low sperm-levels in men, it is recommended to be banned in the US. Exposure to atrazine can be harmful and in extreme cases, can cause health problems[6].

Atrazine has been classified as moderately toxic by USEPA[7]. The United Nations Committee of Experts on Transportation of Dangerous Goods classifies atrazine in Hazard Class 6.1: poisonous substances; and Packing Group III: substance presenting a relatively low risk of poisoning in transport. Lifetime exposure of atrazine above the MCL (maximum contaminant level) of 3 ppb can cause certain types of cancer. Its exposure can affect human tissues such as nerve, muscle, heart and liver.

Atrazine is a potential info-disruptor in vertebrates[8]. It is highly mobile in both terrestrial and aquatic ecosystems. It is resistant to degradation, with a reported half-life of 95-350 days[9] and is found 10 to 20 times more often in water quality monitoring studies than the second most detected pesticide. Atrazine degrades slowly(1-2 years) once in the water column[10]. Atrazine has been shown to interfere with olfactory-related physiological processes in many species[11].

1.1. Pathways for Atrazine in the Environment

Once atrazine is applied, some part may enter the air(via volatilization), some may be washed from the soil by rainfall and enter surrounding areas including streams, lakes, or other waterways and remaining may migrate from the upper soil surface to deeper soil layers and enter the groundwater. In most cases, atrazine breaks down in the soil over a period of one growing season. Atrazine is removed from air mainly by rainfall. When atrazine is on dust particles, the wind can...
brow it long distances from the nearest application area. Atrazine does not tend to accumulate in living organisms such as algae, bacteria, clams, or fish, and, therefore, does not tend to build up in the food chain[11].

1.2. Pathways for Atrazine in the Body

If atrazine containing dust is inhaled, some of the particles may deposit in lungs. Larger atrazine particles may deposit before reaching the lungs and be coughed up and swallowed. If human skin comes in contact with atrazine contaminated soil or water, a small amount of it may pass through skin and into the bloodstream. If one swallows food, water, or soil containing atrazine, most of it will pass through the lining of stomach and intestines and enter bloodstream. Once atrazine enters bloodstream (i.e. is absorbed), it is distributed to many parts of body. Atrazine is changed in our body into metabolites. Some atrazine and its metabolites enter some of organs or fat, but atrazine does not build up or remain in the body. Most of the metabolites leave the body within 24-48 hours, primarily in through urine, with a lesser amount in the feces[11].

1.3. Uptake, Metabolism, and Excretion

Atrazine is almost completely absorbed from the gastrointestinal tract, and only penetrates the skin to a very limited extent. The absorbed herbicide is rapidly eliminated. In the rat, the whole-body half-life is about 1.3 days, and 95% of the dose is eliminated within 7 days[12]. The highest concentration of atrazine and/or its metabolites is found in the red blood cells, to which the triazines bind effectively. The primary route of elimination in rodents is via the urine (about 75%); approximately 20% is eliminated in the feces.

In rats, mice, rabbits, pigs, goats, sheep and chickens, in vitro phase I metabolism of atrazine via cytochrome P-450 yielded the mono- or di-N-dealkyl products. Metabolic phase II conjugation to glutathione compounds was much slower than phase I dealkylation[13].

Absorption from the skin may be relatively low: dermal absorption is concentration dependent and proportionally higher for dilute solutions[14]. In in vitro studies using human skin, about 16% of the applied dose of atrazine was absorbed by the skin[15].

In a study, six human volunteers were occupationally exposed dermally and via inhalation. Metabolism was rapid, with production of equal amounts of the desisopropyl metabolite(2-chloro-4-ethylamino-6-amino-s-triazine, or desisopropylationtrazine) and the fully N-dealkylated metabolite (2-chloro-4,6-diaminom- triazine)[16].

In another study on six workers engaged in the manufacture of atrazine, the doubly dealkylated metabolite comprised 80% of urinary metabolites, whereas only 2% unchanged atrazine was detected[17]. In study on human skin, three-quarters of the applied dose was still retained by the skin after 20 hours, and some metabolism took place in situ; 50% of the total metabolites formed consisted of desisopropylatrazine, with a smaller amount of the diamino deriva-

tive and traces of the deethyl derivative in skin or receptor fluid[14].

1.4. How are People Exposed to Atrazine

People, who rely on surface or groundwater for drinking water and who live downstream from fields where atrazine was applied to crops, may be exposed through contaminated drinking water. The factory worker may be exposed to higher amounts of atrazine. Farm workers and herbicide applicators, who apply atrazine, may be exposed to atrazine because it is used in agriculture. People may be exposed to atrazine by digging in dirt that has atrazine in it. Children may be exposed to atrazine by playing in dirt that contains atrazine. Children may also be exposed to atrazine if they drink water from wells that are contaminated with the herbicide. The various ways of exposure are: breathing, drinking, eating and touching[14].

2. Studies on Atrazine Exposures to Human

The potential health effects for the exposed persons include: congestion of the heart, lungs and kidneys, low blood pressure, muscle spasms, weight loss, damage to adrenal glands, cardiovascular damage, retinal degeneration, muscle degeneration and cancer.

Studies with vertebrates have shown potential atrazine-linked endocrine effects as it increases human aromatase activity in human adrenocortical carcinoma cells in vitro atrazine exposures[18] and also plasma levels of testosterone in male salmon exposed to 3.6 mg/L atrazine[19]. In August 2009, atrazine was prominently featured as a potential cause of birth defects, low birth weights and menstrual problems when consumed at concentrations below federal standards[20].

Atrazine can affect health by altering the way of working of the reproductive system. Studies of couples living on farms affected by atrazine found an increase in the risk of pre-term delivery. Atrazine caused changes in blood hormone levels in animals that affected the ability to reproduce. Atrazine affect the reproductive system in humans by a different mechanism. Atrazine also caused liver, kidney, and heart damage in animals and human. An increased risk of developing mammary tumors was observed in one strain of female rats. Not enough information is available to definitely state whether atrazine causes cancer in humans[21].

Atrazine affects reproductive biology by mimicking or antagonizing the action of hormones. The environmental presence of atrazine has been rarely related to reproductive disturbances in wild mammals[22], birds[23], reptiles[24] and fish[25].

2.1. Major Effects of Pesticides

2.1.1. Fetal Deaths

Reviews by Arbuckle and colleagues concluded that there
is limited epidemiologic evidence for associations between early fetal deaths and some maternal or paternal pesticide exposure indices[26]. In a study, Ontario farm family observed suggestive associations between early fetal deaths and preconceptual phenoxy herbicide or fungicide use (mainly by fathers)[27]. Studies of Chinese textile workers and a U.S. nationwide study found dose-response relationships between early fetal death and prenatal maternal serum p, p′-dichlorodiphenyldichloroethylene (DDE) levels[28].

Studies in California found associations between late fetal deaths and maternal occupational or residential pesticide exposure indices during the first or second trimester[29]. The U.S. nationwide study also found a dose-response relationship between late fetal death and prenatal maternal serum DDE levels[30]. The Ontario study found no association between second trimester fetal deaths and preconceptual or first trimester parental(mainly paternal) phenoxy herbicide exposure[31].

2.1.2. Preterm Birth

There is also evidence of an association between preterm birth and prenatal maternal or cord serum DDT/DDE or β-hexachlorohexane levels and reduced acetylcholinesterase activity levels in cord blood[32].

Birth defects Investigators found limited evidence for associations between parental pesticide exposure indices and neural-tube birth defects (NTDs) and orofacial, limb reduction, and cardiac birth defects[28]. A Minnesota cohort study found an increased risk of NTDs in agricultural regions with the highest use of phenoxy herbicides and fungicides[33].

Several studies demonstrated associations between cryptorchidism and self-reported paternal occupational pesticide exposure[34], but a Danish study found no association[35]. Among the few epidemiologic studies of birth defects using biomarkers of pesticide exposure, cryptorchidism was associated with maternal serum DDT/DDE and hexachlorobenzene levels[36], infant adipose tissue heptachlor and hexachlorobenzene concentrations[37] and with adipose tissue or maternal serum DDE concentrations[37].

In experimental animals, transplacental exposure to the pesticides DDT/DDE, vinclozolin, procyomidone, or linuron produced hypospadias, cryptorchidism, and other abnormalities[38]. Hypospadias was linked to farm expenditures on tractor spraying equipment for grain production. Other studies showed no association with maternal or paternal occupation in farming or gardening[35], maternal serum DDE levels[39], or maternal occupational pesticide exposure[40]. Accessory nipples in male infants were linked to prenatal maternal serum DDE concentrations[41].

2.1.3. Neuropsychologic Function

The few epidemiologic studies in this field are inadequate to assess human risks directly[42]. One such study demonstrated no association between neuropsychologic scores at ages 6 or 12 mo and cord blood DDE concentrations[43]. Another study showed that abnormal neonatal reflexes were associated with elevated prenatal maternal urinary organophosphate metabolite levels[44].

2.1.4. Neurotoxicity

There have been sporadic case reports of severe childhood neurotoxicity (including coma, seizures, and death) after ingestion or excessive dermal exposure to N,N-diethyl-meta-toluamide (DEET), a widely used insect repellent[45]. The U.S. EPA recently requested developmental neurotoxicity data from manufacturers for about 140 pesticides considered to be neurotoxic[46].

2.1.5. Cancer

Childhood brain cancer, leukemia, Wilms’ tumor, neuroblastoma, and Ewing’s sarcoma of bone are associated with parental occupational pesticide exposure[47]. A U.S. cohort study of children of licensed agricultural pesticide applicators found an increased risk of childhood cancer compared to the general population and a greater risk among children whose fathers did not use protective gloves[48].

Several recent epidemiologic studies have increased the evidence for associations between childhood leukemia and lymphoma and paternal occupational pesticide exposure[49]. However, there is some evidence that postnatal pesticide exposure is also linked to childhood leukemia[50]. Five epidemiologic studies each found associations between non-Hodgkin’s lymphoma and one or more pesticide exposure indices, including parental agricultural pesticide use and residential pesticide use[50].

2.1.6. Poisoning

There are over 50,000 reported childhood pesticide poisonings annually in the United States, with about 3000 involving moderate to severe toxicity[51]. The main causes of moderate or severe poisonings were organophosphates, pyrethrins, herbicides, and carbamates. Children poisoned by hexachlorobenzene in Turkey developed severe disease characterized by hyperpigmentation and large bullae in skin areas exposed to sun (caused by the photosensitizing effect of high circulating porphyrin levels); when reexamined as adults, most affected persons had hyperpigmentation, severe scarring of skin, and arthritis[52].

2.2. Other Health Effects

Limited evidence supports an association between early childhood ear infections and biomarkers of perinatal organochlorine pesticide exposures (DDE, hexachlorobenzene)[53]. Potential effects of pesticides on pubertal sexual development in humans remain largely unexplored. A study of male youth living near cashew plantations aerially sprayed with endosulfan reported delayed Tanner stage pubertal development compared to a comparison group from a village remote from the plantations[54].

2.3. Exposure of Children
Children of farmers have the potential to be exposed to agricultural pesticides via the take-home pathway. Children, especially children less than 6 years old, spend more time indoors and on the floors and may be exposed via hand and object to mouth contact. Furthermore, farm children may have the opportunity to be exposed to agricultural pesticides by playing or working in treated fields, contact with treated animals, contact with contaminated farm vehicles, equipment or storage areas, and even through direct handling of pesticides. Parental occupation involving pesticide application has been associated with childhood cancers[48] and household pesticide use has been associated with childhood leukemia[55].

Several papers have been published investigating farm children’s exposure to pesticides using biological monitoring[56-57]. However, only a few have estimated pesticide dose to ascertain the potential health significance of these exposures[58].

Maternal exposure to atrazine in drinking water has been associated with low fetal weight and heart, urinary, and limb defects in humans. It is not known whether atrazine or its metabolites can be transferred from a pregnant mother to a developing fetus through the placenta or from a nursing mother to her offspring through breast milk.

There is a growing body of scientific evidence suggesting that there are critical periods of time extending from conception to puberty when the reproductive[59], immune[60], nervous[61], and endocrine[62] systems in children may be more affected by atrazine exposures. The fetus is more vulnerable to the toxic effects of a number of environmental exposures[63] than are children or adults. At the same time, scientific evidence suggests that the fetal environment may impact the future health of both the child and adult[64].

Studies examining the effects of in utero exposures to environmental contaminant have shown increases in the prevalence of middle ear and pulmonary diseases among infants born to Taiwan women exposed to polychlorinated biphenyls and polychlorinated dibenzofurans through the consumption of contaminated rice oil[65].

Dutch children were found to have a decrease in immune function indices after prenatal exposure to background levels of PCBs and dioxins[66].

The development of allergies or hayfever appeared to be more common in children who had been potentially exposed to pesticides during the pregnancy period, especially in male offspring. Children aged 12 and over had nearly double the odds of having allergies or hayfever if they were exposed in utero to herbicides. Interestingly, a number of studies have shown farm children to have a reduced risk of allergies[67].

The risk of immune system impairment or modulation from some environmental contaminants has been shown to be increased if the exposure occurs in utero or during early infancy. Few epidemiologic studies have examined the association between prenatal pesticide or other environmental exposures and the subsequent development of atopic disease in children[68].

3. Effects on Human Beings

In humans, the decline and well-known regional differences in semen quality[69], the increasing incidence of testicular cancers[70], and increasing rates of developmental abnormalities in male and female reproductive tracts[71] during the last five decades, have been related to atrazine contamination. All these phenomena were called the testicular dysgenesis syndrome. For instance, the consumption of PCB-contaminated fish appears to shorten New York women's menstrual cycles[72].

Atrazine can disrupt endocrine functions in several ways. These include interactions with transport proteins, hormone receptors, metabolic enzymes, and disruption of cell signaling processes. The most studied mechanisms involve receptor-mediated processes. They are reported to affect via estrogen receptor binding. Other actions including interference with human steroid hormone binding globulin[73], increased serum estrogen bioactivity[74], and disruption in gene expression of steroidogenic enzymes[75] have been reported. However, little is known concerning the direct effect of steroidogenic enzymes[76].

Aromatase levels are crucial in various tissues including gonads and implicated in numerous physiological functions, and pathologies such as hormone-dependent cancers for which several classes of inhibitors have been designed[77]. Abnormalities in aromatase expression have been found in a wide range of structural and functional disorders in reproduction, development, cell and sexual differentiation, growth and maintenance of sexual behavior due to atrazine exposure.

Sanderson et al[78] demonstrated that the herbicide atrazine stimulates aromatase activity, in contrast the fungicide Fenarimol and the herbicide Roundup inhibit aromatase activity in the human placenta and in JEG3 cell line, depending on the dose and time of exposure.

Atrazine that inhibits gonadal aromatase activity in developing alligators in vivo at a concentration of 14 ppm[79], and in human adrenocortical carcinoma H295R cells in culture[78], was found to inhibit aromatase activity.

Chu et al[80] noticed that atrazine may affect a number of biological/physiological processes, including disruption of the endocrine system function, lipid metabolism and reproduction. Atrazine and its metabolites were found to contaminate human blood in Japan[81], women mammary fat tissue in Argentina[82] and milk in British mothers (around 0.5–2.3 μg/g)[83].

In humans, immune development begins early in embryonic life and continues throughout the early postnatal period. A number of pesticides, including hexachlorocyclohexane, chlordane, diazinon, DDT, carbofuran and hexachlorobenzene, have been observed to induce developmental immunotoxicity. In utero exposure to DDT has altered primary and secondary humoral immune response, immunoglobulin production, histamine concentrations, and mast cell numbers in animals. Further, these adverse effects are sustained.
3.1.2. Immune System

Atrazine treatment (100 mg/kg body weight) of rats decreased the production of interleukin, a regulatory protein in the immune system; interferon, an immune system protein that fights viral infections; and tumor necrosis factor, a protein that kills tumor cells.

Atrazine reduces the production of interferon by blood cells. Interferon is a protein used by the immune system to fight viral infections. Cultures of spleen cells treated with atrazine produced fewer b-lymphocytes, immune system cells that produce antibodies, than untreated cells[94].

Research into the toxic effects of atrazine exposure has revealed atrazine to be directly disruptive to the central nervous system, the endocrine system and the immune system and found that acute intraperitoneal exposure to atrazine reduced hematopoietic progenitors for a short period. A transient reduction in T-cell reactivity has also been reported after an acute oral exposure. Subchronic (2-week) exposure to atrazine decreased resistance to tumor challenge[95]. Atrazine exposure would decrease target cell adhesion and subsequent granule release. It is reported that atrazine can specifically inhibit the release of lytic granules without affecting the ability of the NK cell to bind to the target cell.

Atrazine has been repeatedly demonstrated to be immuno-toxic both in vitro and in vivo[94]. Alexander et al.[96] reported the effects of a direct 24-h atrazine exposure on human NK cell lytic function by demonstrating that atrazine significantly inhibits human PBL lysis of NK-sensitive targets in a concentration-dependent manner.

Roberge et al.[97] found that atrazine concentrations as low as 10 μM cause reductions in the function of the phosphodiesterase enzyme(PDE) in a cell-free model. PDE is responsible for the conversion of the signaling molecule cyclic adenosine monophosphate(cAMP) to five prime adenosine monophosphate(5′-AMP), and inhibition of PDE can cause increases in the levels of cellular cAMP.

Another possible mechanism of action of atrazine is on the ability of treated cells to form microtubule organizational centers(MTOCs). It is reasonable to assume that MTOC formation would be affected by atrazine exposure considering the decreased levels of granule release. MTOC mobilization in the NK cell is dependant on SRC or SYK/SRC-mediated activation of phosphatidylinositol 3-kinase(P13-kinase) signaling. The P13-K molecule activates Rac and allows for signaling along the extracellular signal-regulated kinase(ERK) pathway[98]. Atrazine affects the ERPK pathway.

3.1.3. Liver and Kidneys

Atrazine can damage both the liver and kidneys. In a study on female pigs fed atrazine at a dose of 2 mg/kg per day for 19 days, researchers noted degeneration of the liver. Liver degeneration also occurred in experiments with rats, but at
higher doses. A study of kidney function found evidence of dysfunction, an increase in the protein content of the urine, in rats treated for 14 days with 10 mg/ kg of atrazine per day[99].

3.1.4. Heart

In a study at a dog, electrocardiograms were altered, and degeneration of the heart muscles occurred. The atrazine breakdown product diaminochlorotriazine also damages the heart. Atrazine’s adverse effects included enlargement and softening of the heart, thickened valves, and lesions[99].

3.1.5. Hormones

Effect of atrazine, its penetrability into mammalian tissues, and its endocrine disrupting potential, leading to hormone-dependent diseases such as cancers or reproductive disorders have been studied[100]. Atrazine affects normal function of human and animal hormone systems. Hormones are biologically active molecules that control growth, development, behavior, and reproduction. Atrazine disrupts a stunning variety of hormone systems including the following:

**Testosterone.** Often called the “male” sex hormone, testosterone promotes the development of male sex characteristics. It is converted into biologically active forms in various organs. A series of studies showed that atrazine inhibits this conversion in male laboratory animals, reducing the amount of the active forms in the pituitary and the hypothalamus. In addition, the number of testosterone receptors in the prostate gland was reduced by atrazine exposure in both young adult rats and older rats. Atrazine also reduces the ability of an active form of testosterone to bind to receptor molecules in the prostate. In addition, exposure to either atrazine or deethylatrazine during nursing decreased the number of testosterone receptors in the prostate of male offspring[101].

**Prolactin.** Prolactin stimulates the production of breast milk in nursing females. Atrazine inhibits “surges” of prolactin that occur during nursing and in response to release of estrogen (“female” sex hormones).

**Progesterone.** Involved in the regulation of menstruation. Progesterone is important during pregnancy. In female rats, exposure to atrazine induced “pseudopregnancies” in which, although the rats were not pregnant, their progesterone levels were high and the animals did not cycle through sexually active phases as they usually do so[102].

**Luteinizing hormone.** Luteinizing hormone is produced in the pituitary gland and regulates the secretion of other sex hormones[103]. Atrazine blocks the “surge” of luteinizing hormone that occurs before ovulation.

**Estrogens.** Often called “female” sex hormones, estrogens regulate the development of sex characteristics and the menstrual cycle, help maintain pregnancy, and prepare the breasts for nursing. Atrazine is not estrogenic; that is, it does not cause certain physiological activities that estrogens cause. Atrazine does not cause increases in uterus weight, as estrogens do, nor does it cause cell division that normally occurs in response to estrogens. However, atrazine does have estrogen related activities. It increases the activity of an enzyme called aromatase that converts testosterone and related hormones to estrogens, and thus could increase estrogen levels.

In a yeast that was genetically modified to produce the human estrogen receptor, atrazine displaced estrogens from the estrogen receptor at low estrogen concentrations, but not at high ones[104]. In addition, the atrazine breakdown product, deethylatrazine, has some estrogenic activity.

**Thyroid hormones.** In rats, atrazine caused a decrease in the blood levels of the thyroid hormone triiodothyronine, a hormone that regulates metabolism and growth[105].

4. Conclusions

It can be concluded that the presence of atrazine in different spheres of environment causes severe effects on human health. These range from those on nervous system, immune system, kidney, heart and liver as well as on hormones and enzymes.

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