



Which exposure stage (gestation or lactation) is more vulnerable to atrazine toxicity? Studies on mouse dams and their pups

Sameeh A. Mansour^{a,*}, Doha A. Mohamed^b, Jean F. Sutra^c

^a Environmental Toxicology Research Unit (ETRU), Pesticide Chemistry Department, National Research Centre, Dokki, Cairo, Egypt

^b Food Science & Nutrition Department, National Research Centre, Dokki, Cairo, Egypt

^c TOXALIM (Research Centre in Food Toxicology), UMR 1331 INRA/INP/UPS, Equipe TMR, BP 93173, 180 chemin de Tournefeuille, 31 027 Toulouse Cedex 3, France

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ABSTRACT

Either during gestation or lactation, the experimental mouse dams received one of the following treatments: (a) diet free of pesticide; (b) diet enriched with atrazine (ATZ); 31.0 $\mu\text{g kg}^{-1}$; (c) diet free of pesticide + oral vitamin E (α -tocopherol; 200 mg kg^{-1} per mouse); and (d) diet enriched with ATZ (31.0 $\mu\text{g kg}^{-1}$) + oral vitamin E (200 mg kg^{-1} per mouse). At the weaning, pups and dams were killed and selected organs and blood samples were collected for analyses. Compared with the control results, ATZ induced alteration in a number of biochemical and histopathological parameters either in the dams or their offspring. The ameliorative effect of vitamin E, based on estimating the "Ameliorative Index; AI" to malondialdehyde (MDA) and superoxide dismutase (SOD) ranged between 0.95 and 1.06 (≈ 1.0) for the dams and the pups either in gestational or lactational exposure routes. In general, the mouse pups were more vulnerable to ATZ toxicity than their mothers and exposure during gestation was suggested to be more effective than during lactation. The findings may support the need to further investigating the adverse effects of exposure to low doses of commonly used pesticides, especially during pregnancy and breast-feeding as well as effects on newborn child.

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1. Introduction

Atrazine, ATZ (6-chloro-*N*-ethyl-*N*-isopropyl-1,3,5-triazinediyl-2,4-diamine; IUPAC) is a chloro-*S*-triazine compound used as a selective pre-emergence and post-emergence herbicide for the control of weeds in a variety of agricultural crops, as well as in forestry and for non-selective weed control on non-crop areas [1]. In 1991, the US-EPA established a Maximum Contaminant Level (MCL)

of 3.0 $\mu\text{g/l}$ for ATZ in drinking water. The most significant regulatory decision in recent years occurred in 2003, after the EU, US, and other nations decided to re-examine the safety of ATZ in light of new evidence. At that time, research had expanded beyond toxicity studies and was beginning to investigate long-term, low-dose exposures in animals, particularly female and fetal animals [2].

Some European countries have included ATZ in the list of pesticide residues to be controlled because it is a potential contaminant due to its chemical characteristics, including lipophilicity, slow hydrolysis, and moderate to low water solubility, and high solubility in organic solvents with high absorption by organic matter, clay and fat tissues

* Corresponding author. Tel.: +20 2 33371211; fax: +20 2 33370931.
E-mail address: samansour@hotmail.com (S.A. Mansour).

[3]. Due to inability to keep water contamination below 0.1 ppb, which is a uniform limit for the residue of any pesticide in drinking and groundwater in the European Union (EU), the EU regulators announced the ban of ATZ use. However, in the rest of the world the use of ATZ continues with few, if any, restrictions, and it is even the most frequently detected pesticide in ground- and surface water of the USA [4].

Possible exposure to ATZ can be assumed due to the application to agricultural land and contamination of surface and ground water [5]. ATZ is readily absorbed through gastrointestinal tract [6]. Occupational exposure may occur through both inhalation and dermal absorption during its manufacture, its formulation and its application by spraying. It is found widely, together with its dealkylated degradation products, in rivers, lakes, estuaries, groundwater and reservoirs. In drinking water, the levels rarely exceed 1 $\mu\text{g/l}$. Surveys of various foods and feeds have generally indicated no detectable ATZ residue. Although ATZ generally has low level of bioaccumulation in fish, it does accumulate in brain, gall bladder, liver and gut of some fishes [7]. Therefore, consumption of contaminated fish can also contribute to human exposure. The residues of ATZ were found in the farmers' blood and urine [8].

The major site for ATZ detoxification is liver, where it is undergoing biotransformation throughout phase I and phase II reactions. In rodent species, two cytochrome P450 (CYP) enzymes (CYP1A & CYP2B) are distinctively involved in ATZ biotransformation [9]. ATZ 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 alters reproductive function not only in human [10], but also in many other species such as developing alligators [11], birds [12], goat [13], and as most vulnerable amphibians [14,15] and fish [16], 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 [17]. Thus, interfering with the biochemical pathways mechanisms including reproductive functions as a whole and also gene expression changes, ATZ inevitably affects biodiversity and causes environmental havoc [18].

With regard to fetal and childhood exposures, the US Department of Health and Human Services arrived at a conclusion that it is not known whether ATZ 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 [19]. In their article, Pathak and Dikshit [17] reported the same ATSDR's awareness. However, Stoker et al. [20] found that 3 h following administration of ^{14}C -ATZ to the Wistar rat, there was a distribution of ^{14}C -chlorotriazines (14C-CITRI) [refer to all residues of the initial dose of ^{14}C atrazine], to the organs of the dam, with the highest amounts in the liver and kidney (1.1 and 0.3% of the administered dose, respectively). Recently, Fraites et al. [21] quantified the distribution of ATZ and its chlorinated metabolites in maternal, fetal, and neonatal fluid and tissue samples following gestational

and/or lactational exposure of Sprague Dawley dams to ATZ at different doses. Dose-dependent levels of chlorotriazines, primarily diaminochlorotriazine (DACT), were present in most samples analyzed, including fetal tissue.

There is growing evidence that exposure to xenobiotics (either pharmaceuticals or environmental chemicals) during gestation may result in a variety of adverse outcomes when the developing organism reaches adulthood. Oral exposure to ATZ is known to alter endocrine and reproductive function in adult and peripubertal rodents of both sexes [22–25], but few studies have investigated the effects of ATZ exposure in utero or during the perinatal period. A number of studies have shown that ATZ can promote oxidative stress, by increasing the concentration of reactive oxygen species (ROS) and products of oxidative damage such as lipid peroxides, and therefore influencing the activity of antioxidant enzymes (AOE) [6,26–28]. Liver is the first target of ingested oxidants and also very important tissue in defense against oxidative stress. Testes also possess proper antioxidant defense, and changes in the activity of antioxidant enzymes have been recorded in xenobiotic-exposed animals [29].

Numerous foods provide vitamin E. Nuts, seeds, and vegetable oils are among the best sources of α -tocopherol, and significant amounts are available in green leafy vegetables and fortified cereals [30]. Vitamin E is the collective name for a group of fat-soluble compounds with distinctive antioxidant activities [31]. Naturally occurring vitamin E exists in eight chemical forms (α -, β -, γ -, and δ -tocopherol and α -, β -, γ -, and δ -tocotrienol) that have varying levels of biological activity [31]. α - (or α -) tocopherol is the only form that is recognized to meet human requirements. The research has not found any adverse effects from consuming vitamin E in food. However, high doses of α -tocopherol supplements can cause hemorrhage and interrupt blood coagulation in animals, and *in vitro* data suggest that high doses inhibit platelet aggregation [32]. Vitamin E is a fat-soluble antioxidant that stops the production of reactive oxygen species (ROS) formed when fat undergoes oxidation. Scientists are investigating whether, by limiting free-radical production and possibly through other mechanisms, vitamin E might help prevent or delay the chronic diseases associated with free radicals. In addition to its activities as an antioxidant, vitamin E is involved in immune function and, as shown primarily by *in vitro* studies of cells, cell signaling, regulation of gene expression, and other metabolic processes [31]. Vitamin E is an important biological free radical scavenger in the cell membranes [33]. Administration of vitamin E at 100 mg kg^{-1} bw to Wistar rats treated with ATZ (300 mg kg^{-1} bw) ameliorated the effects of ATZ suggesting it as potential antioxidant against ATZ-induced oxidative stress [6].

Most studies on ATZ toxicity to rodents during gestation/lactation were carried out on doses much higher than the dose characterized as the "acceptable daily intake, ADI" (0.005 mg kg^{-1} food per day). Examples for the doses used in this respect were 1, 5, 20 and 100 mg kg^{-1} /day [20,21,34,35]; 100 mg kg^{-1} /day [36]; 50–100 mg kg^{-1} /day [37]; and 50–200 mg kg^{-1} /day [18].

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