

## Oxidative Stress of Pesticide Residues Leads to Male Infertility

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### ABSTRACT

Oxidative stress is induced by various pesticides groups. Previous studies suggested that pesticide residues exert oxidative stress as a mechanism of their toxic actions in human or animal's tissues. The ROS produced by metabolites of pesticides can induce disturbances in the oxidative homeostasis through abnormal redox state and depletion of anti-oxidant. Further, ROS may impair cellular proteins and DNA, and lead to cyto-lethality of the cells via disturbance of signaling pathways and inducing apoptosis pathway. Oxidative stress may be created by residues of and can induce multi reproductive organs dysfunction and male disability.

**Keywords:** Oxidative Stress; Pesticide Residues; Testicular Damage; Male Infertility.

## Definition of the oxidative stress

Oxidative stress creates a disturbance in the systemic activity of reactive oxygen species and in the biological system's capability to deal with the reactive metabolites or to ameliorate the inducing impairment. Imbalance between the normal redox state of cells may induce hazard effects through the induction of peroxides and free radicals that impair the cell contents, including proteins, lipids, and DNA. Oxidative metabolism may induce basal oxidation, as well as strand breaks in DNA. Reactive oxygen species generated, e.g.  $O_2^-$  (superoxide radical),  $OH$  (hydroxyl radical) and  $H_2O_2$  (hydrogen peroxide) induced indirect basal damage. In addition, some reactive oxidative species serve as cellular messengers in redox signaling. Though, the normal mechanisms of cellular signaling may be disrupted by oxidative stress [1].

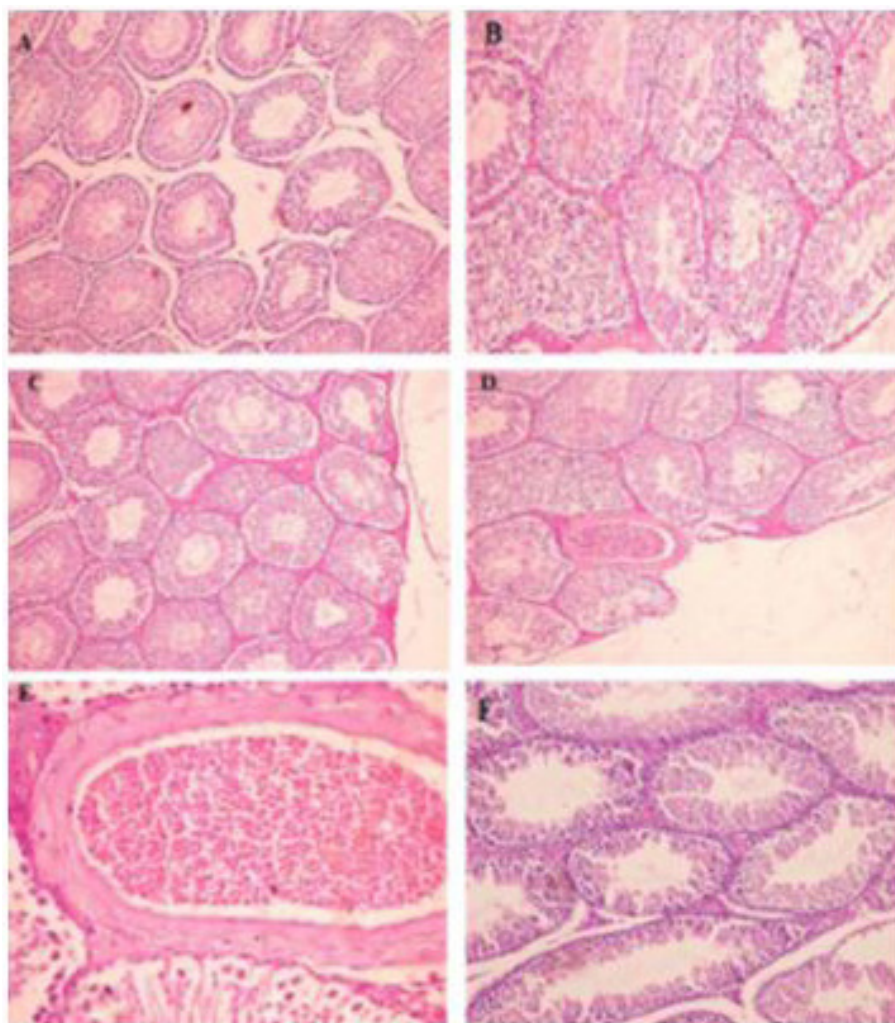
### Many pesticide residues have been reported to induce oxidative stress in living systems.

For instance, acetamiprid caused oxidative stress and mitochondrial damage in Leydig cells and increased malondialdehyde and nitric oxide levels in Leydig cells [2]; similarly, thiacloprid also increased oxidative stress [3]. Additionally, carbendazim [4] and chlorpyrifos have been shown to induce oxidative stress by increasing antioxidant enzyme activities and glutathione content and decreasing hydrogen peroxide and lipid peroxidation levels in the hypothalamus, testes and epididymis of treated rats [5]. Furthermore, a mixture of residues (cyhalothrin and imidacloprid) has been shown to induce testicular oxidative stress in adult albino Wistar male rats [6] and to increase testicular malondialdehyde, catalase, superoxide dismutase, and glutathione-S-transferase activities and to reduce testicular glutathione concentrations [7]. Moreover, profenofos has been shown to induce testicular toxicity in mature male rats [8]. Cypermethrin induced oxidative stress and spermatogonial germ cell apoptosis in rats [9]. Similarly, DDT induced testicular oxidative stress in adult rats and increased lipid peroxidation and metallothionein levels, superoxide dismutase catalase activity, and hydrogen peroxide production [10]. Diazinon has been shown to induce oxidative stress by reactive oxygen species, which may be the reason for sperm DNA fragmentation [11]. Dimethoate has been shown to increase the level of lipid peroxidation and to decrease the activities of antioxidant enzymes in the testes of rats [12]. Endosulfan isomers ( $\alpha$  endosulfan,  $\beta$  endosulfan and endosulfan sulfate) changed the levels of metabolites involved in energy metabolism and oxidative stress, and these were associated with an imbalance in sex steroid hormone synthesis [13, 14]. Glyphosate, an herbicide residue, decreased glutathione levels and superoxide dismutase activity in the testicular tissue of rats [16]. Similarly, exposure to 2,4-dichlorophenoxyacetic acid has been shown to induce oxidative stress and apoptosis in mouse testes [17, 18]. A mixture of glyphosate and zineb produced severe oxidative stress in testicles by affecting the antioxidant contents [19]. Hexachloro-cyclohexane elicited a significant decrease in the activities of cytosolic superoxide dismutase and catalase and ascorbic acid content together with an increase in the levels of lipid peroxidation and hydrogen peroxide [20]. It has been shown that imidacloprid reduced antioxidant activities, increased malondialdehyde content and elevated protein oxidation product levels, with severe histopathological alterations, in rat testes [21]. A mixture of lambda-cyhalothrin and imidacloprid has been shown to increase thiobarbituric acid reactive substance levels, to decrease glutathione levels and to inhibit catalase and superoxide dismutase in Wistar male rats [6].

### This evidence shows the potential risk of male infertility. These impairments testicular damage include the following:

- 1. Mitochondrial damage** in Leydig cells caused by acetamiprid [2], clothianidin [22], cypermethrin [23], carbendazim [4], DDVP damage also is caused in Sertoli cells and germ cells of male rats by 2,4-D [24] and carbofuran and in testicular tissues, reducing the diameter of the seminiferous tubules and number of spermatogonia, primary and secondary spermatocytes and spermatids, as caused by chlordane.
- 2. DNA damage in sperm cells** in male mice has recently been shown to be caused by chlorpyrifos [25], glyphosate. [16],  $\alpha$ -cypermethrin, and imidacloprid [26].
- 3. Oxidative damage of the testes** and testicular tissues in male rats caused by imidacloprid [21] and in the testes of lizards [27].

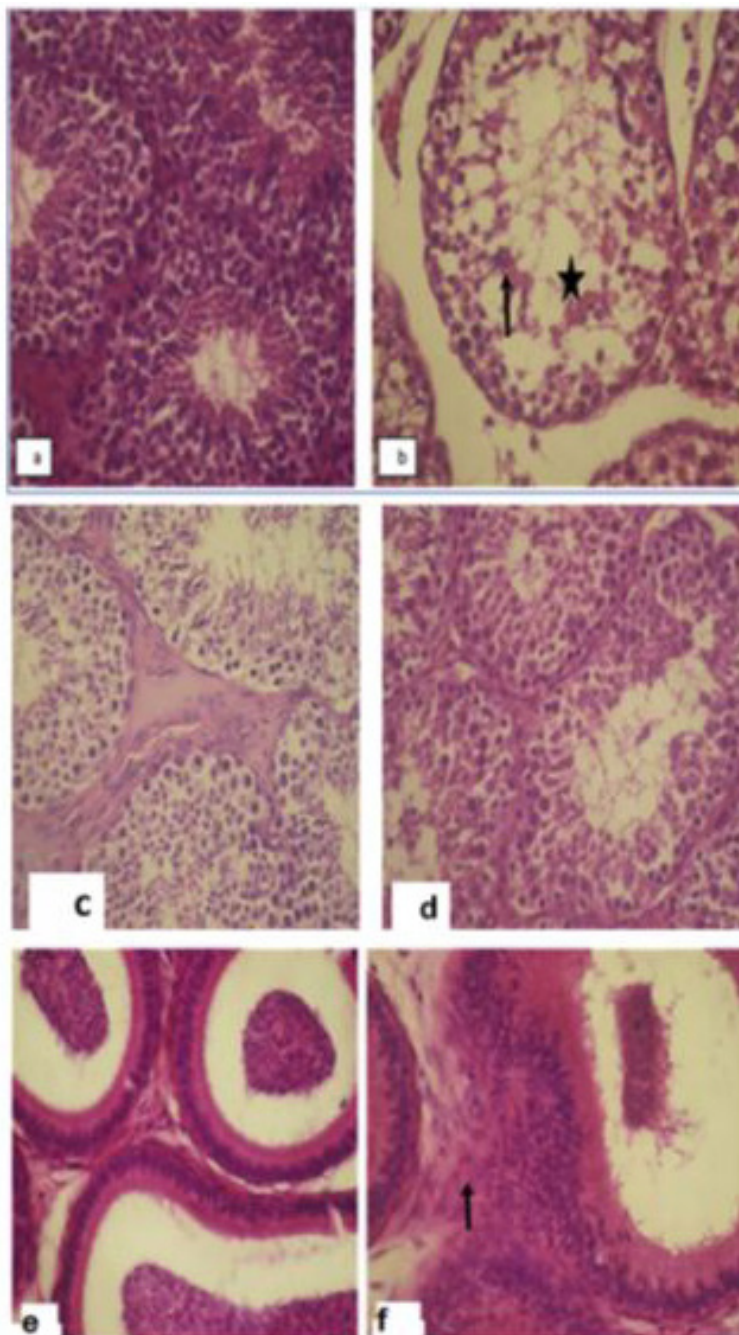
Moreover, herbicide residues have been shown to create similar effects were observed among farmers in rural area in Malaysia. These herbicides are glyphosate [16], trifluralin [28], and 2,4-D [17, 18]. The exposure to chloropyrifos induces depletion in antioxidant defense systems in the testes This effect may lead to disruption in the functional integrity of cell organelles Figure (1) from pervious ours [29]



**Figure 1A:** The seminiferous tubules of the control rats were structurally normal, and they have regular arranged rows of spermatogenic cells at different stages of maturation. **B:** Testes of CPF-treated groups showed seminiferous tubules dissociated from each other with decrease in spermatogenic cells H&E 310. **C:** Interstitial edema is present among the seminiferous tubules from the same group H&E 325. **D:** Severe congestion of the testicular blood vessel, which has thick wall H&E 310. **E:** Thick wall and congested blood vessel associated with proliferating connective tissue H&E 340. **F:** Testes of GSH plus CPF treated group showed seminiferous tubules had mild changes in spermatogenic cells accompanied by mild edema in the interstitial tissues H&E 310 [29]

4. **Necrosis, edema and cellular damage** in testicular tissues of rats have been caused by dichlorvos [30, 31]

5. **Severe seminiferous tubule degeneration** in rats has been caused by dimethoate [32], malathion [33] and hexachlorocyclohexane [20, 34]. The prolonged exposure to mancozeb fungicide altered the male rabbit's reproductive abilities and inducing oxidative stress in testicular homogenate. Disruption of the germinal epithelium with vacuolization of Leydig cells and reduced spermatogenic cells Figure 2 from pervious our work [35]



**Figure 2:** a) testis of control rabbit showed normal histological features with all the successive stages of spermatogenesis and spermatozoa. Leydig cells have a normal appearance in the interstitial tissue. (H & E 40X). (b) testis of mancozeb treated rabbits showed degeneration of spermatogenic cells with massive vacuolation (arrow) formed by exfoliation germ cells (star) and disorganization of interstitial tissue and decreased in the number sperms in the lumen (H & E 40X). (c) testis of mancozeb treated rabbits showed interstitial edema (arrow) and degeneration of Leydig cells, disorganization of spermatogonia and spermatocytes (star). (H & E 40X). (d) testis of (mancozeb and glutathione) treated rabbits showed mild degeneration in spermatogenic cells (arrow) (H & E 40X). (e) epididymis of control rabbits showed more or less normal histologic appearance (H & E 10X). (f) epididymis of mancozeb treated rabbits showed metaplasia of the epithelial lining (arrow) (H & E 40X) [35]

## Conclusion

Several pesticide residues can create oxidative stress that may result in dysfunction in testicular cell organelles and altered male reproductive abilities. This evidence shows the potential risk of pesticide residues to induce male infertility.

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