Effects of Endosulfan on Human Health

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Abstract

Endosulfan is an organochlorine insecticide and acaricide used to control a broad range of insect and arthropod pests on a wide variety of crops in many agrosystems. Endosulfan is readily absorbed by humans via the stomach, lungs and through the skin. It can cause acute and chronic toxicity. Laboratory assays suggested more susceptibility of female than males to the lethal effects of endosulfan. Central nervous system is the main target in endosulfan toxicity. Endosulfan is a neurotoxin, haematoxin, genotoxin and nephrotoxin. Laboratory studies have also shown that there are potential carcinogenic effects. Toxicity of this insecticide on reproductive organs was confirmed. Endosulfan has been linked to congenital physical disorders, mental disabilities and deaths in farm workers and communities across the globe. Symptoms of poisoning include headaches, dizziness, nausea, vomiting, mental confusion, convulsions, hyperactivity, seizures, coma and respiratory depression, in severe cases resulting in death.

Introduction

Endosulfan (6, 7, 8, 9, 10-hexachloro-1, 5, 5a, 6, 9, 9a-hexahydro-6, 9-methano-2, 4, 3-benzodioxathiepin-3-oxide) is a broad-spectrum organochlorine insecticide and acaricide for control of agricultur pests on a variety of field, fruit, and vegetable crops. Endosulfan active ingredient is mixture of two isomers α and β, in the ratio of approximately 70% and 30% respectively (Saiyed et al. 2003). Endosulfan residue has been identified in a variety of environmental media (air, surface water, ground water, soil and sediment) and its metabolites have been reported in human and domestic animals milk (Nag and Raikwar, 2008, Campoy et al. 2001), fruit and vegetable (Mitchell, 1976; Pokharkar and Dethe, 1981). The most likely way for people to be exposed to endosulfan is eating the contaminated food with it. Exposure to endosulfan may occur by breathing, eating, or drinking the substance, or by skin contact (Anonymous, 1002; 2000).

In mammals, commercial endosulfan is transformed into more water soluble metabolites, mostly endosulfan sulfate, followed by ether and diol metabolites. All of these metabolites are bioaccumulated in the adipose tissue, depending on their lipophilicity (Cerilo et al. 2005). Toxicity studies of endosulfan have been conducted in animals. These studies are carried out to identify the target organs of toxicity and possible spectrum of effects. The effects of any chemical substance are determined by the dose, duration and the time of exposure. There is a close similarity between the spectrum of health effects observed in the human population exposed to endosulfan and those described in animal studies. It has been demonstrated that much lower doses of toxicants may result in adverse health effects manifesting as functional or organic disorders in later life if the exposure takes place during the early developmental phase (Anonymous, 2002). Several cases of poisoning have been reported in work place where men have exposed to endosulfan over long periods (Paul and Balasubramaniam, 1997).

In chronic studies, endosulfan was used in oral test by corn oil (Gupta and Gupta, 1977), peanut oil (Gupta, 1978) or as a suspension in water with tragacanth powder (Paul et al., 1992; 1993; 1994). For acute intraperitoneal injection, alcohol or peanut oil was used (Gupta, 1978; Gupta and Gupta, 1977).

Review

Endosulfan acute toxicity

As in the cases of most other pesticides, endosulfan can cause acute toxicity in animals and human beings due to over exposure (Anonymous, 2002). Acute oral toxicity is higher than dermal toxicity (silva and gammon, 2009). Endosulfan poisoning can be suspected in the presence of primary central nervous system manifestations including seizures, with or without clinical or laboratory evidence of other organs dysfunction such as liver failure (Karatas et al., 2006). Symptoms of poisoning include death, clinical signs, irritation of stomach and small intestine, congestion of kidneys, lungs and adrenals, reddening of small intestine, neurotoxicity, erythema, atonia, desquamation, hemorrhagic lung, granular livers, irritation of large intestine, congested kidneys, nausea, vomiting, seizures and dizziness (Karatas et al. 2006; Silva, 2007).

Endosulfan chronic toxicity

The sub-acute and chronic toxicity studies of endosulfan in animals suggest that the kidneys, liver,
immune system, and testes are the main target organs (Paul and Balasubramaniam, 1997). Long term exposure is linked to immunosuppression, neurological disorders, congenital birth defects, chromosomal abnormalities, mental retardation, impaired learning and memory loss (Silva, 2007). Histopathological changes were observed in liver, kidney and muscles of rats when exposed to a mixture of endosulfan various intervals. The examinations revealed hepatotoxic, nephrotoxic and muscular necrotic effects in pesticides exposed rats (Benjamin et al. 2006; Kurutas et al. 2006). Endosulfan alters the activities of some enzymes such as lactic dehydrogenase, glucose-6-phosphate dehydrogenase and alkaline phosphatase, and decreases mitochondrial energy production in mice (Kurutas et al., 2006; Tietz, 1999).

There are some indications that endosulfan can have adverse effects on the immune system at low levels of exposure (Anonymous, 2000). There is mounting evidence that organochlorine compounds can act as hormones. Endosulfan may also be a part of the cause for the disease in the quality of semen, an increase in testicular and prostate cancer, an increase in defects in male sex organs, and increases incidence of breast cancer which has been observed in the last fifty years (Saiyed et al. 2003; Chitra et al., 2001; Singh and Pandey, 1990; Sinha et al., 1995; Soto et al., 2008).

Neurological effects of endosulfan

Neurotoxicity of endosulfan is the primary effect observed both acutely and chronically in both humans and animals. Documented human data have shown the central nervous system to be the major target of endosulfan action (Silva, 2007; Anonymous, 2000). Neurotoxicity of endosulfan has been studied experimentally in tissue cultures (Sunol et al., 2008; Wozniak et al., 2005), invertebrates (Ghiasuddin and Matsumura, 1982; Chen et al., 2006; Bloomquist, 1993) and vertebrates including mammals (Brunelli et al., 2009; Ballesteros et al., 2009; Paul et al., 1992; Cabaleiro et al., 2008; Banerjee and Hussain, 1986). The mechanism of neurotoxicity of endosulfan appears to be dominated by its capacity to inhibit non-competitively the GABA-A type of receptors (Cole and Casida, 1986; Chen et al., 2006), although other targets are believed to exist (Sunol et al., 2008; Paul et al., 1994; Vale et al., 2003). Scremin et al. (2011) suggested that endosulfan induced a large increase of cortical evoked potentials amplitudes at doses that did not elicit convulsions. These responses could be used as a non-invasive diagnostic tool to detect low-level endosulfan intoxication in humans. Exposure has also been linked to conditions such as cerebral palsy, epilepsy and it may increase the risk of Parkinson’s disease (Stoytcheva, 2011).

Toxicity on reproductive system

In recent years, there has been growing concern about toxicity of a number of chemicals, including pesticides, on the male reproductive system (Murray et al. 2001; Sharpe, 2001). Reported effects of endosulfan on the male reproductive system in experimental animals have been variable, depending on species, age at exposure, dose, duration of exposure, and study end points (saiyed et al. 2003). When adult rats were exposed to endosulfan for 10 weeks (5day per week), reduction in intratesticular spermatid counts, sperm abnormalities, and changes in the marker enzymes of testicular activities, such as lactate dehydrogenase, sorbitol dehydrogenase, γ-glutamyl transpeptidase, and glucose-6-phosphate dehydrogenase were shown providing further evidence of effects on spermatogenesis (Khan and Sinha 1996; Sinha et al. 1995). Exposure of younger animals (3 weeks old) showed marked depletion of spermatid count as well as decreased daily sperm production at a dose of 2.5 mg/kg/day (Sinha et al. 1997). More recent studies have shown that exposure of pregnant rats to endosulfan at 1 mg/kg/day from day 12 through parturition leads to decreased spermatogenesis in offspring (Sinha et al. 2001).

Saiyed et al. (2003) undertook a study to examine the relationship between environmental endosulfan exposure and reproductive development in male children and adolescents. The study parameters included recording of clinical history, physical examination, sexual maturity rating (SMR) (including pubic hair, testes and penis) and estimation of serum levels of testosterone, luteinizing hormone (LH), follicle-stimulating hormone, and endosulfan residues. Their study results, after controlling for age, showed significantly lower SMR scores and serum testosterone levels and higher levels of serum LH in the study group compared with controls. Oral administration of the pesticides endosulfan, methyl parathion and mancozeb inhibits compensatory ovarian hypertrophy, decreases the number of healthy follicles, increases the number of atretic follicles, and affects the oestrous cycle in rats (Asmathbanu and Kaliwal, 1997; Dhondup and Kaliwal, 1997; Mahadevaswami et al., 2000). Azarnia et al. (2008) were assessed the effects of endosulfan on ovary structures of 50-day-old BALB/C mice. The endosulfan induced decrease of ovarian size in mice was associated with a decrease in healthy ovarian follicles and corpora lutea, and increased number of atretic follicles. Whether this endosulfan effect is due to a direct effect on the ovary or an indirect effect on the hypothalamus or pituitary, or to a desensitization of the...
Estrogenic Effects of endosulfan

Several xenobiotic such as polychlorinated biphenyls, chlordane, and methoxychlor were shown to be estrogenic in animal models (Soto et al. 1994); however, their lower estrogenic potency was interpreted as having none or weaker deleterious effects on humans exposed through the food chain. Occupational exposure to chlordane, on the other hand, resulted in overt estrogenicity manifested as oligospermia and sterility (Guzelian, 1982).

The estrogenic activity of xenobiotic was assessed by 1) determining the relative proliferative potency (RPP); this is the ratio between the minimal concentration of estradiol needed for maximal cell yield at 6 days and the dose of the test compound to achieve a comparable proliferative effect, and 2) measuring the relative proliferative effect (RPE); this is 100x the ratio between the highest cell yield obtained with the chemical and with estradiol (Soto et al. 1994).

Soto et al. (1994) were used “in culture” bioassay to assess the estrogenicity of endosulfan insecticide. The E-screen test (that measures the proliferative effect of estrogens on their target cells) uses human breast strogen-sensitive MCF7 cells and compares the yield achieved after 6 days of culture in medium supplement with 5% charcoal-dextran stripped human serum in the presence (positive control) or absence (negative control) of estradiol and with diverse concentration of xenobiotic suspected of being estrogenic. Their results showed that technical grade endosulfan and α and β endosulfan isomers were estrogenic at concentrations of 10-25 µM. Higher concentrations were cytotoxic.

Sex-related difference in the toxicities of endosulfan

Acute toxicity studies have indicated that female rats are more highly susceptible than males to the lethal effects of endosulfan (Gaines, 1969; Gupta, 1976). Liver injury that occurred after chronic oral exposure to endosulfan was more marked in female rats in comparison to males (Paul et al., 1995). A slow metabolism of the insecticide in females as compared to male rats accounted for these findings. In support of this suggestion, blood and tissue residue levels of endosulfan were significantly higher in female rats when compared to that in males (Dikshith et al., 1988). Male rats responded more than females to the locomotor stimulating action of chronic endosulfan (2 mg/kg for 90 days) treatment (Paul et al., 1995). A metabolic factor may account for this finding too, if the metabolite endosulfan sulphate is responsible for locomotor stimulation as a result of its greater neurotoxic property than the parent compound (Dorough et al., 1978) and if biotransformation of endosulfan occurs at a much faster rate in males in comparison to females (Paul and Balasubramaniam, 1997).

Genotoxicity of endosulfan

Earlier studies on the genotoxicity of endosulfan have yielded inconsistent results (Pednekar et al., 1987; Scarpato et al., 1996; Chaudhuri et al., 1999; Falck et al., 1999). Bajpayee et al. (2006) in their study, endosulfan and its metabolites were assayed for their ability to induce DNA damage in Chinese hamster ovary (CHO) cells and human lymphocytes. The compounds produced statistically significant (P < 0.01), concentration-dependent (0.25–10 IM) increases in DNA damage in both CHO cells and human lymphocytes. Endosulfan lactone caused the most DNA damage in CHO cells, while the isomeric mixture of endosulfan produced the greatest response in lymphocytes. The results indicate that exposure to sublethal doses of endosulfan and its metabolites induce DNA damage and mutation.

Lu et al. (2000) in their study examined the genotoxicity of α- and β-endosulfan in vitro with a HepG2 cell line. They used sister chromatid exchanges (SCE), micronuclei (MN), and DNA strand breaks as detected by single-cell gel electrophoresis (SCG) assays as biomarkers to judge the genotoxicity of α- and β-endosulfan at concentrations from 1×10-12 M to 1×10-3 M. After treating HepG2 cells for 48 h with β-endosulfan, SCE showed a significant increase at concentrations from 1×10-7 M to 1×10-5 M, and MN showed a significant increase at concentrations from 5×10-5 M to 1×10-3 M. α-Endosulfan failed to show significant effect in both the SCE and MN assays. After treating HepG2 cells with α- or β-endosulfan for 1 h, DNA strand breaks were significantly induced by α-endosulfan at concentrations from 2×10-4 M to 1×10-3 M, and by, β-endosulfan at 1×10-3 M. The results of this study suggest that both α- and β-endosulfan are genotoxic to HepG2 cells and that the genotoxicity of β-endosulfan seems stronger than that of α-endosulfan.

Neurobehavioral effects of endosulfan

Results of receptor binding and biochemical studies have shown that endosulfan has a potential to alter the activities of central cholinergic, dopaminergic and serotonergic mechanisms. Thus considerable interest has been generated in investigating a correlation between endosulfan-induced behavioral aberrations and changes in neurotransmitter activities (Paul and Balasubramaniam, 1997). Endosulfan after chronic exposure at low dose levels produced circling movement (Anand et al., 1985) and stimulation of motor activity in rats (Anand et al., 1985; Paul et al.,
An involvement of dopaminergic mechanism accounted for endosulfan induced hypermotor activity and circling movement, since these effects were suppressed by the antidopaminergic drug chlorpromazine (Anand et al., 1985).

**Bioaccumulation of endosulfan in fatty tissues**

Endosulfan stores easily within the fatty tissues of living organisms. Cerrillo et al. (2005) in their study investigated the presence of \( \alpha \)-endosulfan, \( \beta \)-endosulfan, and its metabolites in fatty and non-fatty tissues and fluids from women in reproductive age and children in Southern Spain. The highest concentration of commercial \( \alpha \)-endosulfan and \( \beta \)-endosulfan was found in adipose tissue, with a mean value of 17.72 ng/g lipids, followed by human milk, with a mean value of 11.38 ng/mL milk. These findings support the lipophilicity of these chemicals and their elimination by milk secretion. The concentration in the placenta homogenate was similar to that in the blood from the umbilical cord (7.74 and 6.11 ng/mL, respectively) and reflected their lower fat content. Endosulfan diol and endosulfan sulfate were more frequently found in placenta homogenate, with a mean concentration of 12.56 and 3.57 ng/mL, respectively, and in blood from umbilical cord, at 13.23 and 2.82 ng/mL, respectively. Botella et al. (2004) determined and compared the levels of 15 organochlorine pesticides in the adipose tissue and blood of 200 women living in Southern Spain. Endosulfan was found in both adipose tissue and serum samples. Among endosulfan metabolites, endosulfan-ether was the most predominant compound in both adipose tissue (68%) and serum (86%) samples. Their results suggested that exposure from mother to child is a common event, both in utero and via breastfeeding, due to the high frequency of exposure of women in reproductive age (Cerrillo, 2005).

**Conclusion(s)**

Endosulfan is a highly toxic chemical and poisonous to most living organisms. The United States Environmental Protection Agency classifies it as ‘highly hazardous’. It has been responsible for hundreds of deaths worldwide, and significant short and long-term human health impacts. Endosulfan kills indiscriminately and is devastating to the environment, contaminating soils, air and water, and damaging mammals and other animals. Endosulfan’s ability for long-range environmental transport, together with its adverse effects supports the need for concerted international action. To date, 62 countries have already voluntarily banned the use of endosulfan. Endosulfan has killed, and will continue to kill and maim if it continues to be legal. National prohibitions on use, together with inclusion under the Stockholm Convention will ensure endosulfan’s eradication from global use and an opportunity to protect people and their shared environment from this deadly chemical.

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