HEALTH IMPACTS AND ECO-TOXICITY OF ENDOSULFAN

INTRODUCTION

Endosulfan, an organochlorine pesticide, is a broad spectrum contact insecticide widely used in pest control. It is used in a wide range of crops including cereals, coffee, cotton, fruit, oil seeds, potato, tea and vegetables. There is a global concern over the acute toxicity of endosulfan. Technically endosulfan is a mixture of two isomers – alpha-endosulfan and beta-endosulfan a mixed proportion of 70% and 30% respectively. The endosulfan residues of toxicological concern are alpha-endosulfan, beta-endosulfan and endosulfan sulfate. The sulphate is regarded as being equally toxic and of increased persistence in comparison with the parent isomers (USEPA-2010). The world Health Organization (WHO) classifies endosulfan in Category 2 (moderately hazardous)\(^1\). United States Environmental Protection Agency (USEPA) classifies endosulfan as Category 1b - highly hazardous\(^2\)The Industrial Toxicological Research Centre (ITRC) in India the nodal centre for the Regional Based Assessment of Persistent Toxic Substances (PTS) for the Indian Ocean region by the United Nations Environment Programme-Global Environment Facility (UNEP-GEF) classifies endosulfan as Extremely Hazardous.\(^3\) The Intergovernmental Forum on Chemical Safety (IFCS) identified endosulfan as an acutely toxic pesticide that poses significant health problems for developing countries and economies in transition.\(^4\) According to the International Programme on Chemical Safety, INCHEM (1998) the Acute oral LD\(_{50}\) (Lethal Dose) for rats is 80 mg/kg and the inhalation LC\(_{50}\) (Lethal Concentration) (1 hour) for rats > 21 mg/L in air. However according to the USEPA the LD\(_{50}\) for oral exposure is 30mg/kg bw and LC\(_{50}\) is less than and equal to 0.5mg/L.

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<tr>
<td>Acute Reference dose (acute Rd)</td>
<td>0.015 mg/kg/day</td>
<td>0.02mg/kg/day</td>
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<tr>
<td>Average Daily Intake (ADI)</td>
<td>0.006mg/kg/day (Referred to as Chronic Reference Dose)</td>
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<tr>
<td>LD(_{50})</td>
<td>30mg/Kg bw</td>
<td>80 mg/kg/day</td>
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Toxicity studies of Endosulfan have been conducted in animals. Animal toxicity studies are carried out to identify the target organs of toxicity and possible spectrum of effects. The effects of any chemical 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 experiments. 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.\(^5\)

The health and ecological hazards caused by exposure to endosulfan has been a global concern. Endosulfan persists in the environment and bioaccumulates in animals and plants, leading to instances of food contamination and eventually dietary exposure in humans\(^6\). Endosulfan's predominant toxicological effect is over stimulation of the centre nervous system, with little or no


\(^5\) Final Report of The Investigation of Unusual Illnesses Allegedly Produced by Endosulfan Exposure in Padre Village of Kasargod District (N.Kerala); NIOH Study

\(^6\) Víctor Briz et al.; Differential estrogenic effects of the persistent organochlorine pesticides dieldrin, endosulfan and lindane in primary neuronal cultures; ToxSci Advance Access published January 27, 2011
Peripheral component. Endosulfan generally has been shown to have higher acute oral and inhalation toxicity than dermal toxicity.\textsuperscript{7} Absorption of endosulfan through the gastrointestinal tract is extremely efficient – around 90\% is absorbed. Similarly, absorption through the skin can be high; as much as 50\%.\textsuperscript{8}

**EXPOSURE TO ENDOSULFAN**

**DIETARY EXPOSURE**
- Ingesting food that has been sprayed with endosulfan
- Drinking water from contaminated ground or surface stores.

**OCCUPATIONAL EXPOSURE**
- Skin exposure or inhalation during pesticide mixing, loading and/or applying a pesticide or re-entering treated sites.

**ACCIDENTAL EXPOSURE**
- Skin exposure or inhalation due to proximity to endosulfan use.\textsuperscript{9}

**VULNERABLE GROUPS**
Some populations are particularly sensitive to endosulfan’s neurotoxic effects; these include unborn children, infants and the elderly. Certain medical conditions also make people particularly sensitive to adverse affects. The Agency for Toxic Substances and Disease Registry (ATSDR) identifies people with liver or kidney disease; pre-existing anaemia or haematological disorders; neurological problems especially seizure disorders; people with HIV/AIDS and people with protein-deficient diets such as the malnourished poor, chronic alcoholics and dieters as vulnerable groups\textsuperscript{10}

**ACUTE TOXICITY OF ENDOSULFAN**
Acute endosulfan poisoning can cause convulsions, psychiatric disturbances, epilepsy, paralysis, brain oedema, impaired memory and death.\textsuperscript{11} Endosulfan is highly toxic and can be fatal if inhaled, swallowed or absorbed through the skin. Acute oral toxicity is higher than dermal toxicity.\textsuperscript{12}

Symptoms of poisoning include hyper activity, excitement, dyspnea (breathing difficulty), apnea (stoppage of breathing), salivation, loss of consciousness, diarrhea, anemia, nausea, vomiting, insomnia, blurred vision, cyanosis (bluish discoloration of skin due to want of oxygen), foaming at the mouth, tremor, dry mouth, lack of appetite, irritability, head ache, decreased respiration, loss of memory, haematuria, albuminuria, confusion, dizziness, imbalance and lack of coordination.\textsuperscript{13}


\textsuperscript{11} ‘Information for the consideration of Endosulfan, Provision of information to the Stockholm Convention Secretariat for use by the POPs Review Committee (POPRC), Pesticide Action Network (PAN) International, 30 June 2008’.


CHRONIC TOXICITY
Exposure through certain conditions of use (e.g. lack of protective equipment), and ‘bystander’ exposure have been linked to congenital physical disorders, mental retardations and deaths in farm workers and villagers in developing countries. The sub acute and chronic toxicity studies of endosulfan in animals suggest that the liver, kidneys, immune system, and testes are the main target organs. A number of neurotoxicity studies were available, primarily in the rat. An acute neurotoxicity study in rats (gavages) showed a greater sensitivity of females compared to males. Long term exposure is linked to immunosuppression, neurological disorders, congenital birth defects, chromosomal abnormalities, mental retardation, impaired learning and memory loss. Long-term oral and dermal exposure in rats has been found to result in rapidly progressive Glomerulonephritis. This is a renal disease that affects the small blood vessels in the kidneys. Long-term oral and dermal exposure in male rats has been observed to cause aneurysms (blood-vessel dilations which if ruptured can even lead to death). Consumption of endosulfan at low dose for longer duration can ultimately lead to differential alterations of Monoamines (an important class of neurotransmitters) in various regions of the rat central nervous system.

There is some indication that endosulfan can have adverse effects on the immune system at low levels of exposure. There is mounting evidence that organochlorine compounds can act as hormones. These compounds, including DDT, PCBs, and endosulfan, may also be 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.

NEUROTOXICITY
In laboratory animals, endosulfan produces neurotoxicity effects, which are believed to result from over-stimulation of the central nervous system. Possible mechanisms of neurotoxicity include (a) alteration of neurotransmitter levels in brain areas by affecting synthesis, degradation, and/or rates of release and reuptake, and/or (b) interference with the binding of neurotransmitters to their receptors. Those exposed over prolonged periods have been found to experience cognitive and emotional deterioration, severe impairment of memory and inability to perform most daily tasks. Repeated exposure to a tolerated dose of endosulfan resulted in a deficit of behavioral responses involving both learning and memory. A serotonergic (activated by or capable of liberating serotonin, especially in transmitting nerve impulses) mechanism appeared to be involved significantly in endosulfan-induced learning impairment and negligibly in its memory disrupting action. Some have also experienced gross impairment of visual-motor coordination. Exposure has also been linked to conditions such as cerebral palsy, epilepsy and it may increase the risk of Parkinson’s disease.

14Endosulfan: Draft Risk Profile; Stockholm Convention on Persistent Organic Pollutants (POPs) Review Committee (POPRC);July 2009
15Memorandum: Revised findings on the health effects of the active ingredient: endosulfan; Office of Environmental Health Hazard Assessment; June 2008
16Information for the consideration of Endosulfan, Provision of information to the Stockholm Convention Secretariat for use by the POPs Review Committee (POPRC), Pesticide Action Network (PAN) International, 30 June 2008
17Galatone, V, Environment Canada (09/01/09) Endosulfan: Canada’s submission of information specified in Annex E of the Stockholm Convention pursuant to Article 8 of the Convention. Available online- http://www.chm.pops.int/, accessed on 05/01/09
18M.K. Lakshamana, T.R. Raju; Endosulfan induces small but significant changes in the levels of noradrenaline, dopamine and serotonin in the developing rat brain and deficits in the operant learning performance; Toxicology 91 1993
21Endosulfan: Draft Risk Profile; Stockholm Convention on Persistent Organic Pollutants(POPs) Review Committee (POPRC);July 2009
22The neurobehavioral toxicity of endosulfan in rats: a serotonergic involvement in learning impairment; V.Paul, E. Balasubramaniam and M. Kazi; European journal of pharmacology; EJPTOX40086 (1994)
IMMUNOTOXICITY
The immune system is adversely affected by endosulfan because exposure decreases the white blood cell count. These cells are vital for functions such as fighting infections, allergies and for tumour suppression. Endosulfan inhibits leucocytes and macrophage migration (this is the inhibition of the natural immune system by disrupting anti-body protection) causing adverse effects on humoral and cell-mediated immune system.

REPRODUCTIVE SYSTEM TOXICITY
There has been a major concern regarding the effect of endosulfan on the reproductive system. It harms the reproductive system by affecting semen quality, sperm count, spermatogonial cells, sperm morphology and other defects in male sex hormones. The study confirmed that endosulfan displayed dose-dependent deformities, behavioural abnormalities and mortality. Detailed studies in adult rats exposed to endosulfan for 5 days per week for 10 weeks showed reduced intratesticular spermatid counts, sperm abnormalities, and changes in the marker enzymes of testicular activities, providing further evidence of effects on spermatogenesis. There is experimental evidence of adverse effects of endosulfan on the male reproductive system, delaying sexual maturity and interfering with the sex-hormone synthesis.

Although the lack of a comparison population in this study makes it difficult to know whether there was an association between endosulfan and infertility, the high prevalence of exposure among women of reproductive age is of serious concern. Pre- and post-natal exposures to endosulfan have been confirmed by measures of residues in human breast milk, placenta, cord blood, and adipose tissue.

ENDOCRINE DISRUPTION
Contradictory opinions on the potential for endocrine disruption have been presented. The latest health effects analysis of endosulfan released by the Stockholm Convention's Persistent Organic Pollutant Review Committee (POPRC) published that in weight-of-the-evidence evaluation by Plunkett (2008) considering all of the available data (published in vitro and in vivo data, published human data, and unpublished toxicological data submitted as part of the pesticide registration process), it was demonstrated that the potency of endosulfan in the available in vitro studies was very low, with potencies in the range of 10⁵ to 10⁶ times less than the naturally occurring hormones and even natural phytoestrogens that are present in the human diet. However there are several studies that prove that endosulfan is an endocrine disruptant. The commission of European union has recently published a priority list of endocrine disrupting substances, placing endosulfan in Group II substance, i.e. a High Production Volume Chemical with

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28 Effect of Endosulfan on Male Reproductive Development (NIOH Study) Habibullah Saiyed et al, volume 111 | number 16 | December 2003 • Environmental Health Perspectives
29 1. Food and Drug Administration. Total Diet Study: Summary of Residues Found Ordered by Pesticide Market Baskets b 91-3 – 97-1, June 1999
3. Shen H et al; Concentrations of persistent organochlorine compounds in human milk and placenta are higher in Denmark than in Finland. Hum Reprod 23(1):201-10.
a potential for endocrine disruption.\textsuperscript{30} It has potential to induce hypo thyroidism.\textsuperscript{31} It competes for estradiol for binding to estrogen receptors, thereby inhibiting hormonal function. The estrogenic potential of endosulfan increases in the presence of other estrogenic organochlorines.\textsuperscript{32} Endosulfan has been shown to have hormone disruption activity on diverse animals ranging from newts to zebrafish. There are disturbing reports suggesting endocrine effect of pesticides including endosulfan on humans. Studies have described impaired thyroid function in pesticide formulators exposed to endosulfan and other pesticides. Estrogenic effects of organochlorine pesticides on human uterine leiomyoma cells in vitro have been demonstrated.\textsuperscript{33} Endosulfan has even shown endocrine-disrupting activity in two different neuronal populations, Cebellar Granular Cells (CGC) and Cortical Neurons (CN) through their direct interaction with neuronal Estrogen Receptors (ER).\textsuperscript{34}

**CONGENITAL PHYSICAL DEFORMITIES**

A relationship has been observed between maternal exposure and foetal malformations in the skull, ribs and spine of rats.\textsuperscript{35} Physical malformations observed in humans include cleft palates, hare lips, club feet, limb malformations, eye deformities and extra fingers and toes.\textsuperscript{36}

**CARCINOGENICITY & GENOTOXICITY**

Role of endosulfan in causing carcinogenicity cannot be conclusively established. However there is considerable evidence that endosulfan can be genotoxic.

It has been found that exposure to sublethal doses of endosulfan and its metabolites induce DNA damage and mutation.\textsuperscript{37} Genotoxicity has been displayed in HepG2 cells (Human liver carcinoma cells)\textsuperscript{38} and hepatocyte-derived transformants.\textsuperscript{39} Endosulfan has caused mutations in bacterial and yeast cell. It is also known to cause mutations in mammals.\textsuperscript{40}

Silva & Beauvais (2010), concluded that endosulfan is considered to be genotoxic on the basis of evidence of genotoxicity in tests for gene mutation, chromosomal aberration and DNA damage in open literature studies, despite other tests being negative.\textsuperscript{41}

A re-analysis data from a 1978 National Cancer Institute, US (NCI) study in Osborne-Mendel rats has revealed that endosulfan induced malignant neoplasms at all sites in male and female rats and

\textsuperscript{31Anon (Nov 12 2001) World Wildlife Fund Comments on reregistration of Endosulfan submitted to Public Information and Record Integrity Branch, Information Resources and Services Division (7502c) Office of Pesticide Programme, Environmental Protection Agency, Washington.}
\textsuperscript{33Report of the committee to study and analyse the effects of aerial spray of Endosulfan in the cashew plantations of PCK Ltd. in Kasaragod district}
\textsuperscript{34V. Briz et al; Differential estrogenic effects of the persistent organochlorine pesticides dieldrin, endosulfan and lindane in primary neuronal cultures; ToxSci Advance Access published January 27, 2011}
endocrine organs in male rats. Both sexes developed lymphosarcomas (a diffused malignant cancer of lymphatic cells of the immune system) and female rats had neoplasms (tumor) of the reproductive system. Endosulfan is also carcinogenic for the liver of female mice.42

No accurate data related to the carcinogenicity of endosulfan in human is available but from field level reports, endosulfan can be highly suspected for having carcinogenic properties in human beings, especially in cases of chronic exposure. In some reports it is referred to as having possible carcinogenic effects, effects in human immune and reproductive system.43 Studies have also shown that it induces proliferation of human breast estrogen sensitive MCF7 cells in vitro which may lead to greater breast cancer risk.44 Studies also indicate the contribution of endosulfan in the combined effect of environmental estrogens in inducing breast cancer.45

TERATOCENICITY
In the studies presented to the Stockholm Convention, no teratogenic effects were identified in animal studies.46 However some studies suggest its teratogenic and carcinogenic properties on rats and mice.47 Therefore, in absence of adequate data, it would be difficult to conclude endosulfan’s teratogenic effects.

BIOACCUMULATION
Endosulfan stores easily within the fatty tissues of living organisms, and it accumulates in concentration whilst exposure continues – that is, the organism absorbs endosulfan at a greater rate than it can be excreted. Studies have shown that both aquatic and terrestrial species can accumulate concentrations of endosulfan to a significant extent48, but the susceptibility to bioaccumulation varies greatly between species – for example, oysters and bivalves appear to accumulate very little endosulfan, whilst some fish species accumulate endosulfan much more readily49. Terrestrial species show a greater relative potential for accumulation than aquatic species, and monitoring data has shown that concentrations of endosulfan have increased over time in beluga whale blubber samples from the Canadian Arctic50, the tissue of freshwater tetra in Brazil51 and even in plants. Two year old conifer needles in Western national parks of the USA were found to have three times the concentration of endosulfan that one year old needles had. This characteristic, teamed with endosulfan’s high toxicity, means there is significant potential for damage.52

43Anon (Dec 2002) Regional Based Assessment of Persistent Toxic Substances- Arctic Regional Report – Chemicals- United Nations Environmental Programme- Global Environment Facility
46Addition information on endosulfan, Stockholm Convention, POPRC 4, UNEP/POPS/POPRC.4/INF/14
47Anon (Feb 2001), Endosulfan Fact sheet (ToxFaqs) Agency for Toxic Substances and Disease Registry (ATSDR), US Dept of Health and Human Services, Public Health Services, Division of Toxicology, Atlanta Georgia
48PAN North America (13/06/00) Endosulfan Deaths in Benin. Pesticide Action Network Updates Service (PANUPS)
49EU Endosulfan proposal. (27/08/08) UNEP/POPS/POPRC.4/14. UNEP. Available online
52POPRC4/5: Endosulfan -
http://chm.pops.int/Portals/0/docs/from_old_website/documents/meetings/poprc/chem_review/Endosulfan/Endosulfan_AnnexD_e.pdf
ECOLOGICAL IMPACT

Technical grade endosulfan is a mixture of two biologically-active isomers, the alpha and beta isomers, which differ in physico-chemical and fate properties. The beta isomer is generally more persistent and the alpha isomer is more volatile. The major transformation products found in the fate studies are endosulfan diol (hydrolysis) and endosulfan sulfate (soil metabolism). Ecological risks are also of concern regarding Endosulfan. The environmental risk assessment suggests that exposure to endosulfan could result in both acute and chronic risks of concern for terrestrial and aquatic organisms. Exposure to endosulfan has resulted in both reproductive and development effects in non-target animals, particularly birds, fish and mammals.

Indiscriminate use of endosulfan plays a significant role in obstructing the catabolic activity of the plants. USEPA recommends that the levels of endosulfan in rivers, lakes and streams should not be more than 74 ppb. But this limit is 15 times more than the concentration required causing reproductive damage in red spotted newt (a common Salamander).

The effects of endosulfan on non-target species can be swift and devastating. Through surface run off, evaporation, or seepage into ground water stores, a variety of wildlife species – as well as humans – can be at risk from its harmful effects. Farmers in Benin have observed birds and frogs dying after eating insects sprayed with endosulfan. Endosulfan is considered to be very toxic to nearly all kinds of organisms. It is highly to moderately toxic to birds and extremely toxic to aquatic organisms (notably fish but also amphibians, shrimp and prawns, aquatic snails and plants and coral reef organisms). Endosulfan has a relatively high potential to bioaccumulate in fish. Endosulfan is classified as highly toxic to birds and mammals on an acute exposure basis and moderately toxic to birds on a subacute dietary basis. Chronic toxicity data on birds and mammals revealed that reproduction and growth were the most sensitive endpoints. In laboratory studies it has also shown high toxicity in rats, and it appears that female rats are 4–5 times more sensitive than male rats.

POTENTIAL FOR LONG-RANGE ENVIRONMENTAL TRANSPORT:

(i) Evidence of long-range environmental transport of endosulfan and endosulfan sulfate is confirmed by Arctic monitoring data;

(ii) Levels of 0.9 and 3.02 ng/g of endosulfan in the blubber of elephant seals in the Antarctic provide evidence of potential concern for endosulfan found in areas distant from its sources of release but the toxicological significance is not known. Other data, however, also show lower levels in other areas of the globe;

(iii) Overall persistence (Pov) for the endosulfan family is in the region of 10 days for tropical air and soil. The Arctic contamination potential after 10 years of continuous releases was between

http://www.epa.gov/pesticides/reregistration/REDS/factsheets/endosulfan_fs.htm, accessed on 12/02/09
54 USEPA; Endosulfan-RED facts; November 2002; EPA-738-F-02-012
55 A. R. Chopade, A.Y. Nalawade, N.S. Naikwade; Effects of pesticides on Chlorophyll content in leaves of medicinal plants; Poll
56 Anon (Feb 2001), Endosulfan Fact sheet (ToxFQAs) Agency for Toxic Substances and Disease Registry (ATSDR), US Dept of
Health and Human Services, Public Health Services, Division of Toxicology, Atlanta Georgia
57 Park D, Hempleman S C, Propper C R (July 2001) Endosulfan exposure disrupts Pheromonal system in the red spotted Newt- A
Mechanism for subtle effects of environmental chemicals. Environmental Health Perspectives 109(7); 669-673.
59 UNEP & GEF (2002) United Nations Environment Programme Regionally Based Assessment of Persistent Toxic Substances: Sub-
60 US EPA (November 2002) Endosulfan RED Facts. Pesticides: Re-registration. Available online-
http://www.epa.gov/pesticides/reregistration/REDS/factsheets/endosulfan_fs.htm, accessed on 12/02/09
61 UNEP & GEF (2002) United Nations Environment Programme Regionally Based Assessment of Persistent Toxic Substances: Sub-
0.1 and 1.0%\textsuperscript{62}.

\textsuperscript{62} Stockholm Convention on Persistent Organic Pollutants POPs Review Committee (POPRC); UNEP-POPS-POPRC.4-POPRC-4-5; Evaluation of endosulfan against the criteria of Annex D