ENDOSULFAN AND NEUROTOXICITY: HUMAN RISK CHARACTERIZATION

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I. Endosulfan and Neurotoxicity: Overview of the Available Data

Endosulfan is a chlorinated cyclodiene broad-spectrum insecticide. It is well-established that the mechanism of action for mammalian toxicity is related to effects of the chemical that lead to stimulation of the central nervous system. For example, high dose intentional, or unintentional, exposures of humans to endosulfan has been associated with convulsions. The mechanism of action of endosulfan has been linked to inhibition of calcium and magnesium ATPase and antagonism of chloride ion transport in gamma-aminobutyric acid (GABA) receptors. As a result, it is not unexpected that neurotoxicity would be en endpoint of concern in endosulfan risk assessment, although it is understood that exposure to low levels of endosulfan in the environment is a different assessment than examination of higher dose occupational exposures and risks, or risks due to ingestion of high doses intentionally (suicide).

There are several sources of data that can be reviewed and analyzed that relate to the potential neurotoxic effects of endosulfan. These sources include the published, peer-reviewed literature, as well as studies submitted as part of the endosulfan pesticide registration process and unpublished. The following is a review of the studies from each source, focusing on the relevancy of the study findings to assessing the risk to human health that may be related to any endosulfan-induced neurotoxicity when exposure is due to low levels of endosulfan encountered in food, soil, and/or water.

A. Published, Peer-Reviewed Studies

1. Studies Reporting *In Vitro* Data

Several studies have been published that have examined the effects of endosulfan *in vitro* on different types of brain cells in culture. Some of these studies were conducted in order to explore the mechanism of action of endosulfan in producing central nervous system stimulation, while others explored some aspect of endosulfan activity on brain cell function. Table 1

below describes the studies, the endpoints examined, and the findings related to endosulfan.

Table 1
***In Vitro* Studies Examining Potential Neurological Effects of Endosulfan**

STUDY TYPE AND CITATION	ENDPOINT EXAMINED	REPORTED EFFECTS
Mouse neuronal cells (15-day old embryos) in culture treated with endosulfan (Pomes et al. 1994. *Neurotoxicology* 15:745-750)	GABA-induced chloride ion flux.	Consistent with known mechanism of toxicity, endosulfan inhibited chloride ion flux at concentrations of 10 μM. LIMITATIONS: Not a toxicity evaluation.
Isolated rat neural stem cells treated with endosulfan (Kang et al. 2001. *J. Vet. Med. Sci*. 63:1183-1190)	Differentiation of neural stem cells, cytotoxicity, cell morphology, apoptosis, MAPK activity, and connexin-43 protein expression.	High doses (20 μM) of endosulfan were cytotoxic. No effect on apoptosis was reported with high dose endosulfan. Endosulfan decreased MAPK activity but also at high doses. LIMITATIONS: Effects only at doses consistent with human blood levels seen in poisoning episodes.
Porcine brain microvascular endothelial cells (model of the blood-brain barrier; BBB) and human glial and neuronal cells in culture (Chan et al. 2006. *Environ. Toxicol.* 21:223-235)	BBB permeability changes and cytotoxicity.	Endosulfan treatment was associated with decreased BBB permeability but not with cytotoxicity to BBB cells. Alpha-endosulfan was selectively toxic to glial and neuronal cells. The cytotoxic dose of alpha-endosulfan was stated by authors to be near the level obtained in brain when rats are injected with 5 mg/kg endosulfan. LIMITATIONS: A non-standard animal species. Effects not directly relevant to human risk assessment.
Human neuroblastoma cells in culture (Jia and Misra. 2007. *J. Appl. Toxicol.* 27:434-446)	Apoptosis induction and cell necrosis.	Endosulfan treatment led to both apoptosis and necrosis in the cells in culture, but only at high doses (100 μM). LIMITATIONS: Effects only at doses consistent with human blood levels seen in poisoning episodes.

Review of each of the studies in Table 1 indicates that, as expected by its chemical class and known mechanism of toxicity, endosulfan had a variety of effects on neurological cells in the various *in vitro* assays. In all cases, the effects elicited by

endosulfan were only seen at doses that would be considered high doses when compared to the level of exposure likely to occur in humans exposed to endosulfan in their environment.[1] Such *in vitro* studies are useful for exploring the mechanism of action of chemicals but are not relevant to human health risk assessment when the exposures of concern are at much lower levels through environmental media.

2. Studies Reporting *In Vivo* Animal Toxicology Data

Over the last three decades, studies have been published that report effects of endosulfan *in vivo* in various laboratory animal species, including the effects of endosulfan on some aspect of neurological function. Table 2 below categorizes and describes the available studies based on the study type, the endpoints examined, and the findings related to endosulfan. It should be noted that many of the studies were performed to elucidate mechanisms of toxicity and were not designed as human health and safety assessment studies.

Table 2
***In Vivo* Administration of Endosulfan in Laboratory Animals and Effects on Neurological Function**

STUDY TYPE	DOSES AND ENDPOINTS EXAMINED	REPORTED EFFECTS
Acute neurotoxicity of endosulfan in rats and mice (intraperitoneal dosing) (Gupta 1976. *Bull. Environ. Contam. Toxicol.* 15:708-713)	Doses of 20-50 mg/kg were determined to LD_{50} values. Doses of 10, 30, and 60 mg/kg. Death and brain acetylcholinesterase levels.	Death was due to CNS stimulation. Brain acetylcholinesterase levels were decreased at doses greater than 30 mg/kg. LIMITATIONS: Older study using a route of administration not relevant to human exposure conditions. Decreases in brain acetylcholinesterase may be questioned

[1] It is well understood that use of *in vitro* doses in the micromolar (μM) range is a "high" dose as compared to levels of chemicals that are usually detected in blood or tissues *in vivo* following dosing of animals and humans. For example, a 20 μM solution of endosulfan if converted to a level in blood or tissue would equate to about 8 mg/L, a high level for a chemical in biological tissues *in vivo*, and in fact is a level associated with high dose intentional poisonings in humans.

		due to age of the study and analytical precision.
Repeat dose effects of endosulfan in newborn rat pups (intraperitoneal study) (Zaidi et al. 1985. *Neurobehav. Toxicol. Teratol.* 7:439-442)	Endosulfan doses of 0, 0.5 or 1 mg/kg i.p., 5 days per week for 3 or 5 weeks, beginning at postnatal day 1. Endpoints examined included cortical brain serotonin receptor binding and fighting behavior (induced by foot-shock).	No effect on either serotonin binding or behavior at 0.5 mg/kg endosulfan. No effect on serotonin binding after 3 weeks dosing with either 0.5 or 1.0 mg/kg endosulfan. Increased serotonin binding with 5 weeks dosing of 1.0 mg/kg endosulfan; increased receptor affinity but not receptor number. Increased fighting behavior with 5 weeks dosing of 1.0 mg/kg endosulfan which persisted for 8 days. Authors report that adults animals treated with 1 mg/kg endosulfan did not exhibit similar responses after 30 days treatment. LIMITATIONS: Older study using a route of administration not relevant to human exposure conditions.
Repeat dose toxicity in adult male rats (oral gavage dosing) (Paul et al. 1992. *Pharmacol. Toxicol.* 71:254-257)	Endosulfan dose of 2 mg/kg for 90 days. Endpoints included assessments of motor coordination, learning ability, and conditioned avoidance responses.	Endosulfan had no effect on motor coordination. Endosulfan treated rats showed decreased learning ability and decreased conditioned avoidance responses. LIMITATIONS: Gavage dosing methods produce pharmacokinetics different from human exposure conditions. Results not consistent with results of guideline studies with endosulfan.
Repeat dose toxicity in immature male rats (oral gavage dosing) (Paul et al. 1994. *Eur. J. Pharmacol.* 270:1-7)	Endosulfan dose of 2 mg/kg for 90 days. Endpoints included assessments of conditioned and unconditioned avoidance responses, and brain 5HT levels.	Endosulfan increased brain 5HT levels. Endosulfan treated rats showed decreased responses (both conditioned and unconditioned avoidance responses). LIMITATIONS: Gavage dosing methods produce pharmacokinetics different from human exposure conditions. Results not consistent with results of guideline studies with endosulfan.
Toxicity of endosulfan in developing rats (oral gavage dosing) (Lakshmana and Raju. 1994. *Toxicology* 91:139-150)	Endosulfan doses of 6 mg/kg from PND 2-25. Endpoints included levels of NE, DA, 5HT in brain and operant learning performance.	Endosulfan treatment was associated with changes in selected brain regions of neurotransmitters (NE and 5HT increased while DA decreased). Endosulfan treatment was associated with deficits in acquisition and retention of memory. LIMITATIONS: Gavage dosing methods produce pharmacokinetics different from human exposure conditions. Results not

		consistent with results of guideline studies with endosulfan. Significant variability in data within treatment groups.
Repeat dose effects of endosulfan alone or combined with methyl parathion in adult Wistar rats (subcutaneous dosing) (Castillo et al. 2002. *Neurotoxicol. Teratol*. 24:797-804)	Endosulfan doses of 0, 0 plus 2 mg/kg methyl parathion, 25 mg/kg, 25 mg/kg plus 1 mg/kg methyl parathion, or 25 mg/kg plus 2 mg/kg methyl parathion. Endpoints examined included spatial learning in a water maze, GABA levels in brain, plasma cholinesterase activity, and biomarkers of renal and hepatic damage.	No significant effects reported in rats exposed only to endosulfan. When administered as a combination, endosulfan and methyl parathion impaired spatial learning in the water maze. LIMITATIONS: Non-standard dosing methods produce pharmacokinetics different from human exposure conditions. Results not consistent with results of guideline studies with endosulfan.
Repeat dose toxicity of endosulfan in juvenile male C57B1/6 mice (intraperitoneal dosing) (Jia and Misra. 2007. *Neurotoxicology* 28:727-735)	Endosulfan administered from PND 5-19 at a dose of 0.155 mg/kg; mice re-challenged at 8 months of age with 1.05 mg/kg for 7 days. Endpoints included dopamine levels in nigrostriatal brain region, acetylcholinesterase levels in cerebral cortex, and alpha-synuclein levels in brain.	Endosulfan decreased dopamine activity but only in mice re-challenged at 8 months. Endosulfan increased brain acetylcholinesterase levels but also only in mice re-challenged at 8 months. LIMITATIONS: Non-standard dosing methods produce pharmacokinetics different from human exposure conditions.
In utero and lactational exposure to endosulfan and effects on prefrontal cortex of male rats (Cabaleiro et al. 2008. *Toxicol. Lett.* 176:58-67)	Dams administered 0.61 or 5.12 mg/kg endosulfan from GD1 to weaning. Pups sacrificed on PND 15 (infant), PND30 (pubertal) and PND 60 (adult). Endpoints examined included levels and activity of amino acids and biogenic amines.	Endosulfan increased amino acid content in infant and pubertal rat brain. Endosulfan decreased GABA and taurine content in adult rat brain. Endosulfan had no significant effects on NE or DA content at any age. Endosulfan increased 5HT content in pubertal and adult rat brain. LIMITATIONS: Changes in brain neurotransmitter activity must be correlated with functional effects due to the complexity of brain function.

Review of the studies in Table 2 reveals that the studies were focused on elucidating aspects of endosulfan's effects on brain neurotransmitter activity of on measures of behavior. As expected, at the doses administered in these studies, in some cases by non-standard routes of exposure for toxicological evaluations (*e.g.,* intraperitoneal dosing), endosulfan had effects on brain

neurotransmitter levels and on behavior. Also as expected, the changes reported in regional neurotransmitter levels in brain were highly variable and showed no consistent patterns that any of the authors related to potential functional changes. As will be discussed in the following section of this paper related to unpublished toxicology data, similar doses of endosulfan administered by more relevant exposure routes (*e.g.,* oral, *in utero* and through lactation) were not associated with long-term changes in either brain morphology or subtle measures of neurologic function, even when animals were exposed during critical periods of brain development. As a result, although high dose exposure to endosulfan may be a risk for neurotoxicity, the results reported in these published studies are not supported by results of studies designed to assess human health risk (guideline toxicity studies), studies that are considered of most relevance when assessing the risk and potential neurotoxic effects of endosulfan exposure through routes encountered in the human environment.

3. Studies Reporting Effects in Humans

With the recognition that humans can be exposed to chemicals such as pesticides both through occupational activities and through contact with environmental media such as food, soil, and water, researchers have become interested in examining the potential for such chemicals to affect the health of human populations. Since it is generally considered unethical to intentionally dose humans with pesticides in order to specifically investigate toxicity, the published literature relating to potential human toxicity of pesticide exposures is limited to observational studies. These are studies where populations are defined not by a specific exposure dose but generally by the likelihood that exposure has or has not occurred. Therefore the data on actual

exposures in any individual within a population being studied is usually inferred, not directly measured. The exception to this would be occupational exposure studies where workers may wear biomonitoring devices that are able to measure either exposure on the skin or exposure in the breathing zone. In some occupational studies, individual measures of internal levels of chemical exposure may be available (*e.g.*, blood, urine). Unfortunately, such human studies where exposure of individuals is reliably quantified are rare. This is a major limitation of human studies in the area of pesticide toxicology and needs to be considered as studies are interpreted. Without adequate exposure information, any reported biological effects are difficult if not impossible to interpret as being related to a particular chemical.

In the case of endosulfan, there are reports of central nervous system toxicity associated with intentional or unintentional poisoning with endosulfan. There are no studies that examined specific aspects of neurotoxicity in humans that might relate to low dose, environmental exposures to endosulfan. The only exception is a recent paper that discussed a link of pesticide exposure to autism (Roberts et al. 2007. *Environ. Health Perspect.* 115:1482-1489). The paper describes a retrospective study based on review of health records in a California Department of Health database. The study was designed to evaluate the association between maternal residence near agricultural pesticide applications during pregnancy and development of autism spectrum disorders (autism) in their children. The authors reported a significant association between application of endosulfan and dicofol and autism diagnoses in children. However, this study lacks any actual exposure data on any of the pesticides specifically examined. This fact combined with the limitations inherent in such studies (lack of a

representative population; classification bias; confounding bias) makes it impossible to determine whether the findings are a true reflection of exposure to endosulfan or any pesticide. In fact, the authors themselves concluded that "The possibility of a connection between gestational exposure to organochlorine pesticides and ASD [autism] requires further study." Considering that no other human studies have reported an association of endosulfan exposure with any type of neurological disease, including autism, provides further evidence that the single paper does not indicate that endosulfan is neurotoxic to humans exposed through their environment.

4. Unpublished Studies

In addition to studies in the published literature, any assessment of the potential neurotoxicity of endosulfan must include consideration of toxicology studies performed as part of the pesticide registration process, studies that are usually unpublished. During the registration process for endosulfan, hazard evaluation and risk assessments performed by regulatory bodies around the world included assessment of neurologic effects. It is a general principle of toxicity testing that potential neurotoxic activity of the test chemical can be assessed through evaluation of a variety of endpoints. Recent regulatory guidance has required submission of rodent developmental neurotoxicity study data, data that are directly relevant to assessing the human health risks associated with chemical exposure.

Although the brain is a target organ following high dose, acute exposures to endosulfan, review of the subchronic (MRID 00145668, 00147182, 41099501) and chronic (MRID 41009502, 40792401) toxicity studies for endosulfan, studies performed in multiple species (*e.g.*, dogs, rats, mice) demonstrates that the brain

is not a target organ for the chemical. The subchronic and chronic toxicity test protocols, as is standard, included evaluations of brain tissues (gross and microscopic) as well as daily clinical observations for signs of behavioral changes in the animals. In these studies, toxic effects generally were reported when endosulfan doses exceeded 2 mg/kg in most species, although there were no reported gross or histopathological changes in the brain in any of the species tested (mice, rats, dogs).

In addition to the subchronic and chronic toxicity studies, reproductive and developmental toxicity studies have also been performed with endosulfan (MRID 43129101 and 00094837). Again, as is standard in these study designs, the studies included evaluations of brain tissues (gross and microscopic) as well as daily clinical observations for signs of behavioral changes in the animals. The data collected were in animals that had been exposed both *in utero* and during lactation, as well as the adult animals which had been directly administered endosulfan. In these studies, toxic effects generally were reported when endosulfan doses exceeded 2 mg/kg in most species, although there were no reported gross or histopathological changes in the brain in any of the species tested (rats and rabbits).

Endosulfan has also been studied in an acute neurotoxicity study in rats (MRID 44403101). This screening level study involving single, high dose exposure to endosulfan is most appropriate for assessing risks due to intentional or unintentional ingestion of high doses of pesticides. As expected, endosulfan exposure was associated with a variety of neurological effects including stilted gait, altered posture, irregular respirations, and decreased spontaneous activity. The lowest doses associated with these effects were 3 mg/kg in female rats and 25 mg/kg in male rats.

In addition to the studies discussed above, a guideline developmental neurotoxicity study was conducted in rats (MRID 46968301). This study is one of the most relevant studies for assessing neurotoxic potential of a pesticide as it involves direct evaluation of animals exposed throughout critical periods of brain development (gestation day 6 through postnatal day 21) and includes both histopathological and functional assessments of neurotoxicity.

In the study, female rats were administered endosulfan in their diet at doses of 0, 3.74, 10.8, or 29.8 mg/kg/day (gestation day 6 through postnatal day 21). Offspring were dosed through passage of drug across the placenta *in utero* and through nursing. The endpoints examined were the standard endpoints for a guideline study and included assessment of dams and offspring. No neurotoxic effects were apparent at the low and middle test dose levels (3.74 and 10.8 mg/kg, respectively). Even at the high test dose (29.8 mg/kg) only minimal effects related to neurotoxicity were noted in either the dams or their offspring. The authors of the study indicated that a no-observed adverse effect level (NOAEL) of 3.74 mg/kg was identified in the study.

Considering the combined unpublished endosulfan toxicity data, the studies show that at relatively high doses as compared to levels of endosulfan that occur in environmental media (*e.g.,* water, soil, food), endosulfan exposure is associated with clinical signs and symptoms of neurotoxicity, but not with long-term, morphological changes in the brain. Therefore, the unpublished endosulfan laboratory animal data when considered together indicate that endosulfan does not pose a neurotoxic risk to human health at environmentally relevant levels of exposure.

II. Does the Weight-of-the-Evidence Indicate that Endosulfan is a Neurotoxic Chemical at Doses Relevant to Environmental Exposure in Humans?

Considering all of the available data, published *in vitro* data, published *in vivo* data, published human data, and the toxicological data submitted as part of the pesticide registration process for endosulfan, a weight-of-the-evidence evaluation can be performed. Such evaluations are routinely performed by regulatory bodies as well as independent scientists when attempting to answer questions concerning the relevance of toxicological data or observations collected in cells or laboratory animals to predicting the toxicity potential of a chemical for humans. Such evaluations are based on patterns in the data that may be present, on the reliability of studies used in the assessment, on the consideration of the limitations of the individual studies used in the evaluation, and on consideration of the relevance of the data to human physiology and human exposure situations. Such evaluations can also rely on data collected for similar chemicals, if such data exists, as a way to fill data gaps in the assessment.

In the case of endosulfan, the *in vitro* studies indicated that endosulfan had some effects on neurotransmitter activity and/or receptors in cultured neurological cells. *In vitro* studies, however, are only relevant as indicators of the potential binding of a chemical to such receptors or indicators of the potential to affect neurotransmitter activity. This is because the conditions of *in vitro* assays do not allow for the known relationship of pharmacokinetics and metabolism to the pharmacodynamics of chemical responses and chemical toxicity. Further, in the case of neurological function, such isolated assays have limited predictive value for the conditions of living organisms where regulation and even development of neurological function is complex. Therefore, the *in vitro* studies with endosulfan are useful for identifying the need for collection of *in vivo* data that should be evaluated for potential effects on neurologic function.

When evaluating the *in vivo* toxicological data, the types of studies and the dose levels administered must both be considered. The studies performed to support the registration of endosulfan (unpublished studies) were consistent in showing that

endosulfan did not produce long-term changes in neurologic function or morphology, even following lifetime exposures or exposures during critical periods for brain development (*e.g., in utero* and postnatal). These studies, like all such guideline *in vivo* toxicology studies, were designed purposely to be valid and realistic assessments of possible effects in humans. Therefore, regulatory bodies rely on such studies to make decisions regarding safe levels for human exposure. The published *in vivo* animal studies that did report effects of endosulfan on neurologic function, however, were not always designed in order to provide such realistic assessments of possible effects in humans. For example, many of the studies employed gavage dosing or intraperitoneal dosing, methods of dosing which result in a pattern of exposure that is not directly applicable to assessing risks from exposure to endosulfan in environmental media. Effects on the brain or on neurologic function were reported only when doses were at levels that were much higher than the levels likely to be encountered in the human environment. Further, reported changes in regional neurotransmitter levels were highly variable and not linked to functional changes. When considered together, the weight-of-the-evidence of the *in vivo* animal studies indicates that endosulfan does not pose a risk to human health based on neurotoxic effects, and that effects observed were limited to situations where exposure conditions were unrealistic as compared to likely human exposures.

In a typical assessment of potential to produce harm in humans, the process of evaluation would be complete after consideration of the *in vitro* and *in vivo* laboratory data. However, in some cases, human data are also available and should be part of the evaluation process. In the case of endosulfan, the one available human epidemiological study does not provide cause-and-effect evidence that endosulfan has toxic effects on the brain. The study lacked the exposure data necessary in order to draw conclusions regarding exposure to any chemical at all, including endosulfan. Therefore, consideration of the human data does not change the conclusions drawn from the laboratory data.

In conclusion, after consideration of all of the available data, the weight-of-the-evidence indicates that endosulfan does not pose a neurotoxic risk to human health at environmentally relevant levels of exposure.

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