DOES ENDOSULFAN MEET THE POP CRITERIA FOR INCLUSION IN THE ANNEXES TO THE STOCKHOLM CONVENTION?

Introduction

The European Commission on behalf of the European Community proposed, on July 26, 2007, to add endosulfan to the relevant Annexes of the Stockholm Convention. The proposal (UNEP/POPS/POPRC.3/INF/9) was verified by the Secretariat (UNEP/POPS/POPRC.3/INF/10) with the conclusion that the subject proposal contains information as required under Annex D 1 (a) and related to the screening criteria set out in Annex D, 1 (b-e). It should be noted that the Secretariat did not refer in its verification to Annex D, 2 of the Convention.

However, POPRC-3 agreed during the meeting to suspend the consideration of listing endosulfan under Annex D, and resume its evaluation at POPRC-4, scheduled for October 13 to 19, 2008.The reason for the postponement was that essential new information was not being made available.

Makhteshim Agan Industries (MAI), a member of Crop Life International, appreciates the effort and consideration the European Commission has put into the drafted proposal for endosulfan, and welcome the opportunity to comment on it and provide additional information for review at the upcoming POPRC-4 meeting (see attached bibliography of study submission). The insecticide, endosulfan, is highly regulated, and the risk assessments for endosulfan are particularly challenging given its long history and large database. The endosulfan registrants committed substantial resources over the last two decades to generate a comprehensive database in the areas of ecotoxicology, environmental fate and risk assessments in addition to ongoing stewardship programs.

Many of the data (published and proprietary) referred to in the dossier have been reasonably summarized. However, in many instances the interpretations are based on data of poor integrity. Information from publications of unknown quality is often used instead of GLP Guideline-studies, which are available for the most important risk assessment endpoints. Worst case scenarios/data are used in place of a "weight of evidence approach"; and last but not least, a quantitative risk assessment (toxicity endpoints versus the available exposure information) is missing as required under Annex D, 2: "*The proposing party shall provide a statement of the reasons for concern including, where possible, a comparison of toxicity or ecotoxicity data with detected or predicted levels of a chemical resulting or anticipated from its long-range transport, and a short statement indicating the need for global control*."

The following is a brief summary of our assessment for endosulfan applying the Annex D criteria of the Convention. The Attachment provides a more detailed review with the appropriate references:

Overview

MAI is a major producer and registrant of endosulfan products for use in agricultural pest management. MAI notes that a thorough review of the drafted proposal does not provide sufficient evidence that endosulfan meets the Annex D criteria; therefore, proceeding with a technical review of the subject proposal under Annex D is not justified. This position is supported by the following evaluation, which demonstrates that all four UNEP-POP screening criteria set out in paragraph 1 and 2 of Annex D of the Stockholm Convention have not been met. We understand that the process for adding new chemicals to the POP treaty is transparent and based on sound data. This process considers scientifically valid risk evaluations using best estimates of exposures to humans and the environment.

Persistence (Criteria => *DT50 in water > 2 months or DT50 in soil > 6 months or DT50 in sediment > 6 months ; or evidence that the chemical is otherwise sufficiently persistent to justify its consideration within the scope of this Convention).*
The draft dossier (UNEP/POPS/POPRC.3/5) refers mainly to laboratory study results or values generated under artificial conditions, and poor study designs (Stumpf et al. 1995; Gildemeister and Jordan, 1984, Gildemeister 1985). More recent guideline soil metabolism studies were not considered (Buerkle 2002; Hammel 2004; Schnoeder 2002). In the case of persistency in water, the proposal refers to an abiotic hydrolysis study with a half-life of greater than 200 days in highly acidic water (pH 5), conditions that do not represent natural habitats where microbial degradation occurs (Goerlitz and Rutz 1989). Results from relevant field dissipation studies demonstrate half-lives of 26 to 169 days under a variety of actual field conditions (Baedelt et al. 1992a, Baedelt et al. 1992b, Tiirmaa et al. 1993; Tiirmaa and Dorn 1988, U.S. EPA 2002). Also data from arctic monitoring programs indicate that endosulfan shows no persistence or accumulation (Mackay and Arnold 2005). Considering the results from all degradation studies, it is concluded that **the criteria for persistence have not been met.**

Bio-accumulation (Criteria => *bio-concentration factor BCF > 5000 or bio-accumulation factor BAF >5000, or in the absence of such data that the log Kow >5; evidence that the chemical presents other reason of concern, such as high bio-accumulation in other species, high toxicity or ecotoxicity; or biomonitoring data in biota indicating that the bio-accumulation potential is sufficient to justify its consideration within the scope of this Convention).*
The log Kow values for endosulfan are below the trigger value of 5 (Sarafin and Asshauer 1987; Muehlberger and Lemke 2004). A listing of all the available fish bioconcentration studies, demonstrate BCF values ranging from 1,000 to 3,000 based on the highest quality studies (Hansen and Cripe 1991; Schimmel et al. 1977; US EPA 2007). In one bioconcentration experiment, where a BCF value of 11,600 was reported (Jonssen and Toledo 1993), a closer analysis of the study demonstrates that the results of the experiment were calculated using an extrapolation from a yellow tetra fish study that was terminated after 28 days based on a static-renewal exposure system without any analytical confirmation of the test solution. Bioconcentration factors for aquatic invertebrates are a factor of 10 lower than those reported for fish (Schimmel et al. 1977). Uptake of endosulfan from food (trophic transfer) compared to uptake from water is less substantial (De Lorenzo et al. 2002). Studies in natural environments (microcosm, farm ponds) demonstrated bioaccumulation values (BAF) for total endosulfan of 100 to 1,500 (Cornaby et al. 1987, Pennington et al. 2004, Schanne 2002). Bioconcentration in terrestrial animals is even less likely than in aquatic organisms, as demonstrated in long-term feeding and kinetic animal studies (Peatman et al. 1999, Reynolds 1996). Since endosulfan is rapidly eliminated (within a few days) after initial uptake (Jonssen and Toledo 1993), the risk of toxicity caused by bio-concentration is very low. Considering the results from all bio-

accumulations studies, it is concluded that **the criteria for bioaccumulation have not been met**.

Potential for long-range environmental transport <u>(Criteria</u> => *measured levels of the chemical in locations distant from the sources of its release that are of potential concern; monitoring data showing long-range transport; environmental fate properties and /or model results that demonstrate long-range transport; half-life in air >2 days).*

Based on endosulfan's vapour pressure (<1,000 Pa; 1.9 x 10^{-3} Pa for alpha, and 9.2 x 10^{-5} Pa for beta-endosulfan), and using the current version of the relevant calculation model, AOPWIN™, half-life values of less than 2 days have been calculated (Buerkle 2003). Arctic monitoring publications indicate the potential for long-range transport of endosulfan residues (AMAP 2004; Vorkamp et al. 2004; Fisk et al. 2005). More recent assessments that analyzed the significance of temporal and spatial exposure levels of endosulfan in various media and remote locations, confirm a high degree of uncertainty regarding the interpretation and quality of the data (10 to 20-fold difference between the mostly used GC/ECD method compared to the more accurate GC/MS method, and very limited number of biotic samples). Therefore, the validity of the published monitoring data at very low trace levels (ppq) needs further independent analytical verification and more comprehensive evaluation (Kelly 2006). New data indicate that there is no spatial or temporal increase of endosulfan residues in the Arctic environment (Hung et al. 2005; Li and Macdonald 2005). The reports do not point to a potential increase of exposure. Even if the reported values are considered for real, the values are far below values that would be expected to produce any ecological or human health effects. There is no consistent reporting of a steady increase of concentration versus time at one location. Tentative results of limited biotic sampling show concentrations in lipids at pg g^{-1} to ng g^{-1} levels, in water at the pg to the low ng L^{-1} levels, and in air at pg m^{-3} to ng m^{-3} levels (Mackay and Arnold 2005). There are no residue findings, which show repeated contamination of the annual fresh snow layer in the Arctic over several years, or an endosulfan concentration increase in the soil of higher cold altitudes. It is very uncertain that long-range transport of endosulfan occurs at relevant levels and to a significant extent.

Considering the results from the long-range transport studies, it is concluded that **the criteria for long-range transport have only partially been met.**

Adverse Effects <u>(Criteria</u> => *Evidence of adverse effects to human health or the environment; or toxicity or ecotoxicity data that indicate the potential for damage to human health or the environment*).

While endosulfan is highly toxic to mammals, and aquatic organisms, the reported concentrations (trace levels), even if verified, would not *adversely* affect human health and/or the environment. The No-Observed-Adverse-Effect-Levels (NOAELs) for endosulfan in aquatic, avian and mammalian tests are orders of magnitude above the published exposure concentrations. Endosulfan demonstrates relatively low bioaccumulation in aquatic and terrestrial organisms; thus, the potential risk to biological receptors is insignificant (Mackay and Arnold 2005).

Considering the results from mammalian and ecological effects studies, it is concluded that the **criteria for adverse effects have not been met**.

Discussion

The EC proposal to consider endosulfan as a POP candidate for further technical review under Annex D of the Stockholm Convention is not supported. In our opinion the draft dossier for endosulfan provides a good overview of most available technical data. The endosulfan data base is comprehensive in terms of toxicity endpoints and exposure data. However, it should be noted that recent data have not been included in the assessment (the attached bibliography of submitted study reports list all the documents that have been submitted separately to the UNEP Secretariat for review and consideration).

The data in these reports should be considered to ensure a more complete and up-to-date assessment. In addition, MAI is deeply concerned with the proposal's evaluation and interpretation using nominally worst-case data instead of applying a more appropriate "weight-of-evidence" approach. The data are often chosen from laboratory studies (conducted under artificial conditions) even when "real life" data from higher Tier systems were available. Frequently, the cited data were considered without a data quality and integrity check (in many cases publications or second hand references were used). The vast amount of scientific information that has been generated worldwide for different authorities, following strict guidelines and requirements, meeting established data quality standards (GLP) ensuring replicability of test results, is often used as a "supplemental" and not as a "core" database. Consequently, the assessment leads to significant bias in the presentation of only selected data that have not been subjected to a standard quality review.

POPRC is well aware that the review process should apply sound Risk Assessment principles as required by the Convention under Annex D, 2 (…*comparison of toxicity or ecotoxicity data with detected or predicted levels of a chemical resulting or anticipated from its long-range transport..),* instead the endosulfan proposal followed Hazard Assessment principles. The proposed evaluation only reflects on selected intrinsic properties of the substance without taking into account potential exposure levels (measured or estimated) and comparing them to toxicity endpoints of the most sensitive organisms, and thus fails to estimate the potential risks for humans and the environment.

Conclusion

We believe that a technical review by the POPRC under Annex D of the Stockholm Convention is not justified given the draft dossier by the EC. Based on a realistic and data set of high quality, endosulfan does not meet the screening criteria set out in paragraph 1 and 2 of Annex D to the Convention. We request that the provided comments be considered in the POPRC review process, and offer continued cooperation with the POPRC to ensure a high standard and quality of the information is made available for inclusion in the endosulfan dossier.

ATTACHMENT

DOES ENDOSULFAN MEET THE POP CRITERIA FOR INCLUSION IN THE ANNEXES TO THE STOCKHOLM CONVENTION?

When a high-quality and objective data set is used including data from higher-tiered studies, the assessment shows that endosulfan does not fullfil the criteria for a POP under the Stockholm Convention, and thus cannot cause unacceptable impact in remote areas.
MAI feels that all available high-quality data should be taken into account for the POP evaluation process ensuring a fair and scientifically objective evaluation process.

PERSISTENCE
Criteria: *DT50 in water > 2 months or DT50 in soil > 6 months or DT50 in sediment > 6 months ; or evidence that the chemical is otherwise sufficiently persistent to justify its consideration within the scope of this Convention.*

Criterion	**Criterion met?**	**Remarks**
In water	 Yes* No No No No No	Hydrolysis in freshwater : T ½ >200 days at pH 5 T ½ < 11 - 19 days at pH 7 T ½ > 4 – 6 hours at pH 9 (Goerlitz and Rutz 1989) Hydrolysis in seawater: T ½ = 3.1 – 2.0 days at pH 8 T ½ = 1.9 – 1.3 days at pH 8.2 Seawater/sedim. System: T ½ = 8.3 – 22 days at pH 7.3 – 7.7 (Cotham and Bidleman 1989; Stumpf 1990)
In sediment	No	T ½ = 18–21 days (Gildemeister 1985)
In soil (Lab tests) Alpha endosulfan	No	T ½ = 28 days (Gildemeister and Jordan 1984; Buerkle 2002; Hammel 2004; Jonas 2002, Schnoeder 2002)
In soil (Lab tests) Beta endosulfan	No	T ½ = 157 days
In soil (Lab tests) Endosulfan sulfate	No	T ½ = 117 – 138 days
In Soil (Field Studies) Total endosulfan (Alpha + Beta + sulfate)	No	T ½ = 26 – 169 days (Baedelt et al. 1992, US EPA 2002a) No accumulation was measured applying endosulfan consecutively over several years (Tiirmaa et al. 1993; Tiirmaa and Dorn 1988) Not persistent or accumulating in remote areas (Mackay and Arnold 2005)

*The following quote was used regarding the dicofol POP assessment (US EPA 2002b): *Based on information from long-term monitoring of water bodies, the mean pH in Europe is 7.4, versus 7.3 for the US. Both regions had about 10% of the sites with a mean pH below 6. Therefore we (EPA) think it is reasonable to use pH 7 rather than a pH 5 data point.*

The only criteria that clearly meets the given persistence criteria for POP is based on an abiotic hydrolysis study at a pH of 5 (Goerlitz and Rutz 1989). But in view of long-term monitoring of pHs in natural water bodies, the measured pHs are between 7 and 8. Therefore, endosulfan does not meet the persistence criteria for water.

Half-lives from laboratory studies in soil are generally below the POP trigger of 180 days. The cited old laboratory degradation study with calculated half-life values of 288 to 2,241 (Stumpf et al. 1995) is considered invalid because of experimental deficiencies (Buerkle 2002). Microbial mineralization of the chlorinated bicyclic carbon skeleton (common molecular part of endosulfan and its identified metabolites) can only be attained if measures are taken to maintain the microbial activity of the soil microorganisms throughout the study period (Jonas 2002; Schnoeder 2002). In order to maintain the biological activity of the soil samples throughout a year, small amounts of new soil from the original sampling location was repeatedly added to the incubation flasks. Norbornene-^{14}C-labelled endosulfan sulfate, known as the major soil metabolite and being slower degraded than the parent substance was used as test substance. Up to 35 % of ^{14}C-labelled CO_2 indicated that the norbornene structure had degraded to a significant extent. The calculated half-lives for the sulphate in soil ranged from 117 to 138 days (Buerkle 2002).

Results from field dissipation studies carried out in Europe and North America resulted in soil half-lives of 26 to 169 days (US EPA 2002a, Baedelt et al. 1992). There is no soil accumulation of endosulfan, even after excessively high application rates over many years. Long-term field accumulation studies with yearly application rates of 5.5 to 12.5 kg endosulfan per ha over a period of 5 to 7 years in different regions, have also shown that endosulfan dissipates within 6 months after the last application to a total residue level in the top soil (0-10 cm) of less than 0.1 ppm (Tiirmaa and Dorn 1988; Tiirmaa et al. 1993). Also data from arctic monitoring programs indicate that endosulfan shows no persistence or accumulation in remote areas (Mackay and Arnold 2005).

Hence, based on the results of high quality lab and field dissipation studies **endosulfan and its metabolite endosulfan sulfate do not meet the criteria for soil persistence**.

BIO-ACCUMULATION

Criteria: *bio-concentration factor BCF > 5000 or bio-accumulation factor BAF >5000, or in the absence of such data that the log Kow >5; evidence that the chemical presents other reason of concern, such as high bio-accumulation in other species, high toxicity or ecotoxicity; or biomonitoring data in biota indicating that the bio-accumulation potential is sufficient to justify its consideration within the scope of this Convention.*

Test	Criterion met?	Remarks
Log Kow	No	Log Kow: 3.1 – 4.8 (Sarafin and Asshauer 1987; Muehlberger and Lemke 2004)

Bioconcentration (fish)	No*	BCF (lab): 2,800 – 11,600 (Ernst 1977, Hansen and Cripe 1991; Schimmel et al. 1977, Toledo and Jonsson 1992; US EPA 2007) BCF (lab): 11,600 (Jonsson and Toledo 1993) BAF (field studies): 100 – 1,500 (Cornaby et al. 1987, Schanne 2002)

***** BCF of 11,600 (Jonsson and Toledo 1993)

The log Kow values for endosulfan are below the trigger value of 5. Among the aquatic organisms, fish seems to be the most sensitive for bioaccumulation testing. Uptake of endosulfan from food (bioaccumulation, biomagnification) compared to uptake from water (bioconcentration) is less important (De Lorenzo et al. 2002). Bioconcentration in terrestrial animals is even less likely than in aquatic organisms, as demonstrated in long-term feeding and kinetic animal studies (Peatman et al. 1999, Reynolds 1996).

The published data on endosulfan bioconcentration and bioaccumulation have to be viewed with caution because of data quality issues; i.e. of the 11 studies reviewed by US EPA (2007), none passed the established quality criteria (US EPA 2007). Taking the highest quality studies into consideration the measured BCF values are below the POP trigger of 5,000 (1,000 to 3,000 in fish compared to 600 or less in invertebrates), with the exception of one bioaccumulation study in yellow tetra fish of 11,600 (Jonsson and Toledo 1993), where the BCF was calculated based on uptake and elimination kinetics from a 28-day exposure period. In the setting of more realistic field studies the measured BCFs were between 100 and 1,500 (Rajendran and Venugopalan 1991; Cornaby et al. 1989; Schanne 2002). Because of rapid elimination (Half-life of 2 - 4 days) there is no bioconcentration via the food chain and less risk of bio-accumulation (DeLorenzo et al. 2002, Mackay and Arnold 2005, Vorkamp et al. 2004). The BCF predictions from bioaccumulation modeling with aquatic organisms range from 1,000 (mean prediction) to 2,400 (90^{th} percentile; US EPA 2007).

Long-term feeding studies in cows, sheep, dogs, rats, and mice along with toxicokinetic studies confirm that the biological half-life of a single dose of endosulfan was 2 days. After repeat administration the biological half-life in blood was approximately 7 days (Christ and Kellner 1968, Deema et al. 1966, Dorough et al. 1978, Gorbach et al. 1968, Kellner and Eckert 1983, Scheuplein et al. 2002). Total endosulfan residues in cows declined with a half-life of 7 days for adipose tissue and 3 days for milk and other tissues once feeding was terminated (Chin and Stanovick 1994, Gupta and Ehrnebo 1979, Leah and Reynolds 1996, Maier-Bode 1966, Peatman et al. 1999, Reynolds 1996). In a 28-day toxicokinetic study in rats, a steady state concentration in blood and tissues was achieved by day 23. At day 28, treatment was stopped, and at the end of the treatment-free period, residue levels in blood and tissues indicated that over 90% of the total administered dose had been eliminated (Needham et al. 1998). If endosulfan was bioaccumulating in mammals, no steady-state would have been reached and residue levels would have been eliminated much more slowly.

Taking all of the available results and its limitations into consideration, it can be concluded that there is no evidence of significant bioaccumulation or biomagnification in the food chain. Thus, **the criteria for bioconcentration have not been met.**

POTENTIAL FOR LONG-RANGE ENVIRONMENTAL TRANSPORT

Criteria: *measured levels of the chemical in locations distant from the sources of its release that are of potential concern; monitoring data showing long-range transport; environmental fate properties and /or model results that demonstrate long-range transport; half-life in air >2 days.*

Criterion	Criterion met?	Remarks
Half-life in air <2 days	No	Based on 1.9 x 10^{-3} Pa (alpha), 9.2 x 10^{-5} Pa (beta), calculation value below criterion using current version of QSAR model AOPWIN™, which used measured rather than estimated increments for all parts of the molecule. (Buerkle 2003)
Monitoring data showing long–range transport	Yes	Trace levels were reported in remote regions like the Great Lakes (highest concentration: 28.5 ppg), the Arctic (4.1 ppq), and mountainous areas were reported; (AMAP 2004; Hung et al. 2005; Li and Macdonald 2005; Muir et al. 2004; Kelly 2006); however, potential analytical difficulties at these trace levels (interferences) and data quality issues are evident.
Measured data of potential concern in remote areas	No	Arctic monitoring studies show that values are far below any ecological or human health effects. (Mackay and Arnold 2005)

The half-life values used in the draft dossier are based either on an out-dated QSAR calculation method according to Atkinson (1987) with larger uncertainty intervals due to estimated increments or on values derived under very specific experimental conditions that cannot be transferred to realistic environmental circumstances (Palm and Zetsch 1991). Estimates conducted with AOPWIN v1.88 resulting in a photo-oxidative DT50 of 47.1 hours (1.96 days) assuming an OH• concentration of 0.5 x 106 cm-3 in 24 hours per day and 1.3 days for an OH• concentration of 1.5 x 106 cm-3 in 12 hours per day (Buerkle 2001). It is noted that there is some uncertainty surrounding the estimated DT50 in air related to the estimation method, the determination of the OH• reaction rate and variation in OH• concentration. As a result, it can be concluded that the atmospheric half-life of endosulfan is shorter than two days (Buerkle 2003).

Endosulfan may be transported via air currents to remote areas (AMAP 2004). The validity of the published monitoring data at very low trace levels (lipids at pg g^{-1} to ng g^{-1} levels, water at the pg to the low ng L^{-1} levels, and air at pg m^{-3} to ng m^{-3}), and needs further independent analytical verification (Kelly 2006). Apparently some of the older results generated with a GC/ECD instead of a GC/MS analytical method, showed significant interferences as a confounding factor (e.g. co-elution from other analytes). No spatial or temporal trend of endosulfan concentrations in the environment of the Arctic is observed (Hung et al. 2005; Li and Macdonald 2005).

There are no residue findings, which show repeated contamination of the annual fresh snow layer in the Arctic over several years, or an endosulfan concentration increase in the soil of higher cold altitudes. It is very uncertain that long-range transport of endosulfan occurs at relevant levels and significant extent (Mackay and Arnold 2005). The highest endosulfan levels reported were found in water samples from temperate lakes in south-central Canada at mean concentrations ranging from 1.3 to 28.5 pg L^{-1} (Muir et al. 2004). There is no evidence of a bioaccumulation or magnification of endosulfan in the food web.

Based on the very low exposure levels in food, water and the environment, no potential concern regarding adverse effects to human health and the environment exists. Therefore, **the criteria for long-range transport have only partially been met.**

ADVERSE EFFECTS

Criteria: *Evidence of adverse effects to human health or the environment; or toxicity or ecotoxicity data that indicate the potential for damage to human health or the environment*

Acute toxicity to aqueous organisms

Test species	**Test type**	**Conc. [µg/L or ppb]**	**Criteria met ?**	**Remarks** Risk calculation (RQs) are based on highest exposure level found =28.5 pg L^{-1} (28.5 ppq or 0.0285 ppt or 0.0000285 ppb)
Fish freshwater	96-hour LC_{50}	0.37 – 2.1	No	RQ = 0.0000285/0.37 = 0.000077
Fish estuarine/marine	96-hour LC_{50}	0.1 - 0.32	No	RQ = 0.0000285/0.1 = 0.000285
Freshwater invertebrates	48-hour EC_{50}	6 – 166	No	RQ = 0.0000285/6 = 0.00000475
Estuarine/marine invertebrates	96-hour EC_{50}	0.45 - 460	No	RQ = 0.0000285/0.45 = 0.000063

Chronic toxicity to aqueous organisms

Species	**Test type**	**LOEC [µg/L or ppb]**	**Criteria met ?**	**Remarks** (s.a.)
Fish freshwater	life cycle incl. early life stage	0.056 - 0.4	No	RQ = 0.0000285/0.056 = 0.00051

Invertebrates freshwater	21 days	< 7	No	RQ = 0.0000285/7 = 0.00000407
Estuarine/marine invertebrates	21 days	< 0.5	No	RQ = 0.0000285/0.5 = 0.000057

Mammalian toxicity

Species	**Test type**	**Endpoint**	**Results**	**Criteria met ?**	**Remarks**
Rats	acute oral LD_{50}	mortality	10 mg/kg b.w. (females) 40 mg/kg b.w. (males)	No	*
Rats	2 generation reproduction	decreased body weight	NOAEL = 15 ppm or 1.2 mg/kg/d LOAEL = 75 ppm or 6.2 mg/kg/d	No	*
Rats	Chronic/ oncogenicity	decreased body weight	NOAEL = 15 ppm or 0.6 mg/kg/d LOAEL = 75 ppm or 2.9 mg/kg/d	No	*

*No risk based on measured or expected exposure levels (highest in water: 28.5 ppq; in air:15 pq m^{-1})

Endosulfan is highly toxic to mammals, and aquatic organisms. However, the compound is not a carcinogen nor a reproductive toxin nor a teratogen and not a mutagen (US EPA 2002). The most recently completed developmental neurotoxicity study with endosulfan clearly demonstrated that there is no evidence of any neuro-developmental effects, and there is no proof that the sperm production (count, motility, morphology) was affected at any dose level (Anderson and Facey 2007). This is contrary to the Secretariat's Proposal under *"Adverse Effects"*, referring to reduced sperm production in mammals.

Endosulfan is not an endocrine disruptor as demonstrated in the available in-vitro and in-vivo GLP studies (Bremmer and Leist, 1998). Until evidence of the contrary has been shown, it seems to be pre-mature to classify endosulfan as a potential endocrine disruptor in both terrestrial and aquatic species. The dossier noted: *An evaluation of that endpoint should await commonly accepted test procedures for determining effects.*

Compared to the lowest toxicity level for aquatic species, i.e. chronic NOEC (fish full life cycle test, 260 days) = 56,000 pg/l or 0.056 ppb (Dionne, 2002), the reported findings in seawater are significantly lower by at least 3 orders of magnitude (between highest exposure and lowest toxicity level). Endosulfan concentrations in arctic terrestrial wildlife, fish and seabirds are below effect threshold levels (Fisk et al. 2005). Taking the highest measured concentration of

0.0000285 ppb from a lake in southern Canada (Muir et al. 2004) into consideration for this assessment, the calculated Risk Quotient (RQ) is 0.00051.

Therefore, it can be concluded that the No-Observed-Adverse-Effect-Levels (NOAEL) for endosulfan in aquatic, avian and mammalian tests performed to date are orders of magnitude above the published exposure concentrations. Also in view that endosulfan demonstrates relatively low bioaccumulation in aquatic and terrestrial organisms, the potential risk to biological receptors seems insignificant (Mackay and Arnold 2005).
Therefore, the criteria **for adverse effects have not been met**.

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