First Phase of Impact Assessment on Endocrine Disruptors:

How to screen which chemicals would fall under different options for criteria to identify endocrine disruptors

EU Conference on Endocrine Disruptors, Brussels, 1st June 2015

www.jrc.ec.europa.eu

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Scope of the screening methodology

- To assess in a limited amount of time the potential endocrine disrupting properties of approximately 700 substances subject to:
  - Plant Protection Products Regulation (PPPR) (approx. 400)
  - Biocidal Products Regulation (BPR) (approx. 100)
  - REACH Regulation
  - Cosmetics Regulation
  - Water Framework Directive (WFD)

Sample of approx. 200 substances

- Apply the four policy options for criteria for identifying EDs in EC Roadmap based on available data

CAVEATS

- Does not substitute full evaluations of individual substances to be carried out by appropriate bodies in the future
- Does not pre-empt the regulatory conclusions that may eventually be made on the basis of such evaluations
- Screening methodology – **best estimate** of which substances falling under the different ED IA policy options

Option1. No policy change.

Interim criteria set in the BPR and the PPPR to be applied.

Substances are or may be considered as EDs if they are or have to be classified as:

- CLP "carcinogenic category 2" and "toxic for reproduction category 2", or
- CLP "toxic for reproduction category 2" and "toxic effects on the endocrine organs"

Substances not fulfilling above criteria will be considered not ED according to interim criteria

Option 2. EDs identified according to WHO/IPCS definition

An endocrine disrupter is an exogenous substance or mixture ***that alters function(s) of the endocrine system**** *and consequently causes* ***adverse health effects*** *in an intact organism, or its progeny, or (sub)populations" (IPCS/WHO, 2002).*

Two elements**: adversity** and ***endocrine disrupting mode of action**

Need evidence for both

Option 3: WHO definition and additional categories

Option 3 proposes two additional categories based on the strength of evidence for fulfilling the WHO/IPCS definition:

- Cat I (fulfils WHO definition, equivalent to option 2)
- Cat II (suspected ED) –evidence insufficient to place in Cat I
- Cat III (endocrine active substance) –evidence insufficient to place in Cat II

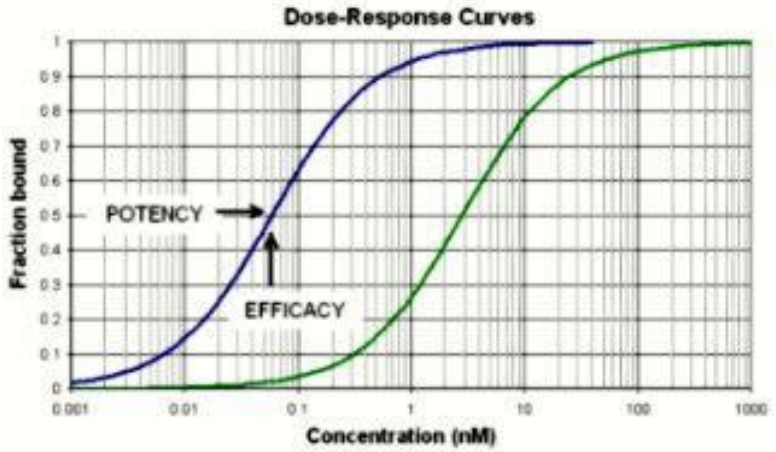
Option 4: WHO definition with the inclusion of potency

Potency refers to the amount of substance necessary to produce a certain effect. A substance A which produces an effect at 5 mg is 10 times more potent than a substance B which produces the same effect at 50 mg.

Applying a potency cut-off at 10 mg,

Substance A confirmed ED

Substance B not considered ED



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Data Gathering: sources & strategy

Rely on already existing readily accessible information

Primarily: evaluated data from the existing regulatory assessment reports***, including*** EFSA conclusions, MS Draft Assessment Reports, REACH restriction dossiers, Support documents for identification of SVHC, opinions of Scientific Committee on Consumer Safety.

Supplemented by additional information: gathered from databases focusing on endocrine effects including non-regulatory studies such as JRC's Endocrine Active Substances Information System, TEDX, SIN list, ToxCast, and in case data are still lacking by targeted literature searching

Types of data to be captured

- Focus on endocrine effects from tests for which OECD Test Guidelines have already been developed
- Production/action of steroid hormones (estrogen, testosterone) impacts on reproduction, fertility, abnormalities in development, onset of puberty)and thyroid hormones (impact on growth and development)
- *In vitro* and *in vivo* mechanistic assays inform on endocrine mode of action
- Mammalian toxicity: reproductive toxicity, carcinogenicity and repeated dose toxicity
- Ecotoxicology: focus on mammals, fish and amphibians (birds to a limited extent)

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Data Template

Information sheet 2-2-2015.xlsx - Microsoft Excel niet-commercieel gebruik

E15 | 1988

	A	B	C	D	E	F	G	H	I	J	K	L	M	N
1	Compound:	Thiram												
2	CAS:	137-26-8												
3	CLP:													
4														
5	Type of toxicity study	Category of toxicity study	Study type (OECD/EPA guidelinenon-guideline)	Study guideline deviations	Reporting date	Reference/source	Species	Strain or in vitro model	Sex	Generation	Number of animals per dose	Dose administered	Unit_dose	Route of administration
6		Drop-down list	Drop-down list											
7	Mammalian toxicity	Repeated dose toxicity	FSTRA		22 March 1988	ECHA	Rat	Crl:CD(SD)BR	M		10	0, 3.5, 38 and 67	mg/kg bw	oral (food)
8	Mammalian toxicity	developmental toxicity	OECD TG 414: Prenatal Developmental Toxicity Study		1988	EFSA-DAR	rabbit		F		16	0, 1, 3, 10	mg/kg bw/day	Oral gavage
9	Aquatic toxicity	Long-term toxicity to fish	OECD Guideline 210 (Fish, Early-Life Stage Toxicity Test)		2008	ECHA	Fish	Pimephales promelas	F			0.56, 1.1, 2.3,	µg a.i./L	Water
10	Aquatic toxicity	Long-term toxicity to fish	OECD Guideline 210 (Fish, Early-Life Stage Toxicity Test)		2008	ECHA	Fish	Pimephales promelas	F			0.56, 1.1, 2.3, 4.5, 9.0	µg a.i./L	Water
11	Aquatic toxicity	Long-term toxicity to fish	OECD Guideline 215 (Fish, Juvenile Growth Test)		2001	ECHA	Fish	Oncorhynchus mykiss	F/M			12, 20, 31, 50 and 80	µg a.i./L	Water
12	Aquatic toxicity	Long-term toxicity to fish	OECD Guideline 215 (Fish, Juvenile Growth Test)		2001	ECHA	Fish	Oncorhynchus mykiss	F/M			12, 20, 31, 50 and 80	µg a.i./L	Water
13	Aquatic toxicity	Long-term toxicity to fish	OECD Guideline 215 (Fish, Juvenile Growth Test)		2001	ECHA	Fish	Oncorhynchus mykiss	F/M			12, 20, 31, 50 and 80	µg a.i./L	Water
14	Terrestrial toxicity	Toxicity to birds	OECD Guideline 206 (Avian Reproduction Test)		1995	ECHA	Bird	Colinus virginianus				100, 500, 2500	mg a.i./kg feed	oral (food)
15	Mammalian toxicity	Repeated dose toxicity	EU Method B.26 (Sub-Chronic Oral Toxicity Test: Repeated Dose 90-Day Oral Toxicity Study in Rodents)		1988	ECHA	Rat	Crl:CD(SD)BR	Male		10	0, 3.5, 38 and 67	mg/kg bw for females	oral:feed
16	Mammalian toxicity	Repeated dose toxicity	EPA OPP 82-1 (90-Day Oral Toxicity)		1990	Exp Key Repeated dose toxicity: oral.003	Dog	Beagle	Female/Male			0.00, 1.94, 2.58, 6.17-7.85, 10.55-14.69		oral:feed
17	Mammalian toxicity	Repeated dose toxicity	Comparable to guideline study		1989	Key Repeated dose toxicity: oral.004	Mouse	CD-1	Male		10	0, 51-58, 101-115, 177-226 mg/kg bw for males	mg/kg bw	oral:feed
18	Mammalian toxicity	Repeated dose toxicity	Comparable to guideline study		1989	Key Repeated dose toxicity: oral.004	Mouse	CD-1	Female		10	0, 59-66, 111-127, 221-281	mg/kg bw	oral:feed
19	Mammalian toxicity	Repeated dose toxicity	Comparable to guideline study		1988	Exp Key Repeated dose toxicity: oral.005	Dog	Beagle	Male		2	4, 16 and 26-15	mg/kg bw	oral:feed
20	Mammalian toxicity	Repeated dose toxicity	Comparable to guideline study		1988	Exp Key Repeated dose toxicity: oral.005	Dog	Beagle	Female		2	4, 16 and 26-15	mg/kg bw	oral:feed
21	Mammalian toxicity	Repeated dose toxicity	EPA OPP 82-2 (Repeated Dose Dermal Toxicity -21/28 Days)		1992	Exp Key Repeated dose toxicity: dermal.001	Rabbit	New Zealand White	Male		5	0, 100, 300, 1000	mg/kg and day	Dermal
22	Mammalian toxicity	Repeated dose toxicity	EPA OPP 82-2 (Repeated Dose Dermal Toxicity -21/28 Days)		1992	Exp Key Repeated dose toxicity: dermal.001	Rabbit	New Zealand White	Female		5	0, 100, 300, 1000	mg/kg and day	Dermal
23	Mammalian toxicity	Repeated dose toxicity	EPA OPP 82-2 (Repeated Dose Dermal Toxicity -21/28 Days)		1992	Exp Key Repeated dose toxicity: dermal.001	Rabbit	New Zealand White	Male		5	0, 100, 300, 1000	mg/kg and day	Dermal
24	Mammalian toxicity	Repeated dose toxicity	EPA OPP 82-2 (Repeated Dose Dermal Toxicity -21/28 Days)		1992	Exp Key Repeated dose toxicity: dermal.001	Rabbit	New Zealand White	Female		5	0, 100, 300, 1000	mg/kg and day	Dermal
25	Mammalian toxicity	Toxicity to reproduction	EPA OPP 83-4 (Reproduction and Fertility Effects)		1991	Exp Key Toxicity to reproduction.001	rat	Charles River Crl:CD® VAF/Plus®	Male		26	0, 1.52, 2.94 and 8.88	mg/kg/day	oral:feed
26	Mammalian toxicity	Toxicity to reproduction	EPA OPP 83-4 (Reproduction and Fertility Effects)		1991	Exp Key Toxicity to reproduction.001	rat	Charles River Crl:CD® VAF/Plus®	Female		26	0, 2.27, 4.61 and 13.89 [partially visible]	mg/kg/day	oral:feed

Data | Evaluation | lists | Validation

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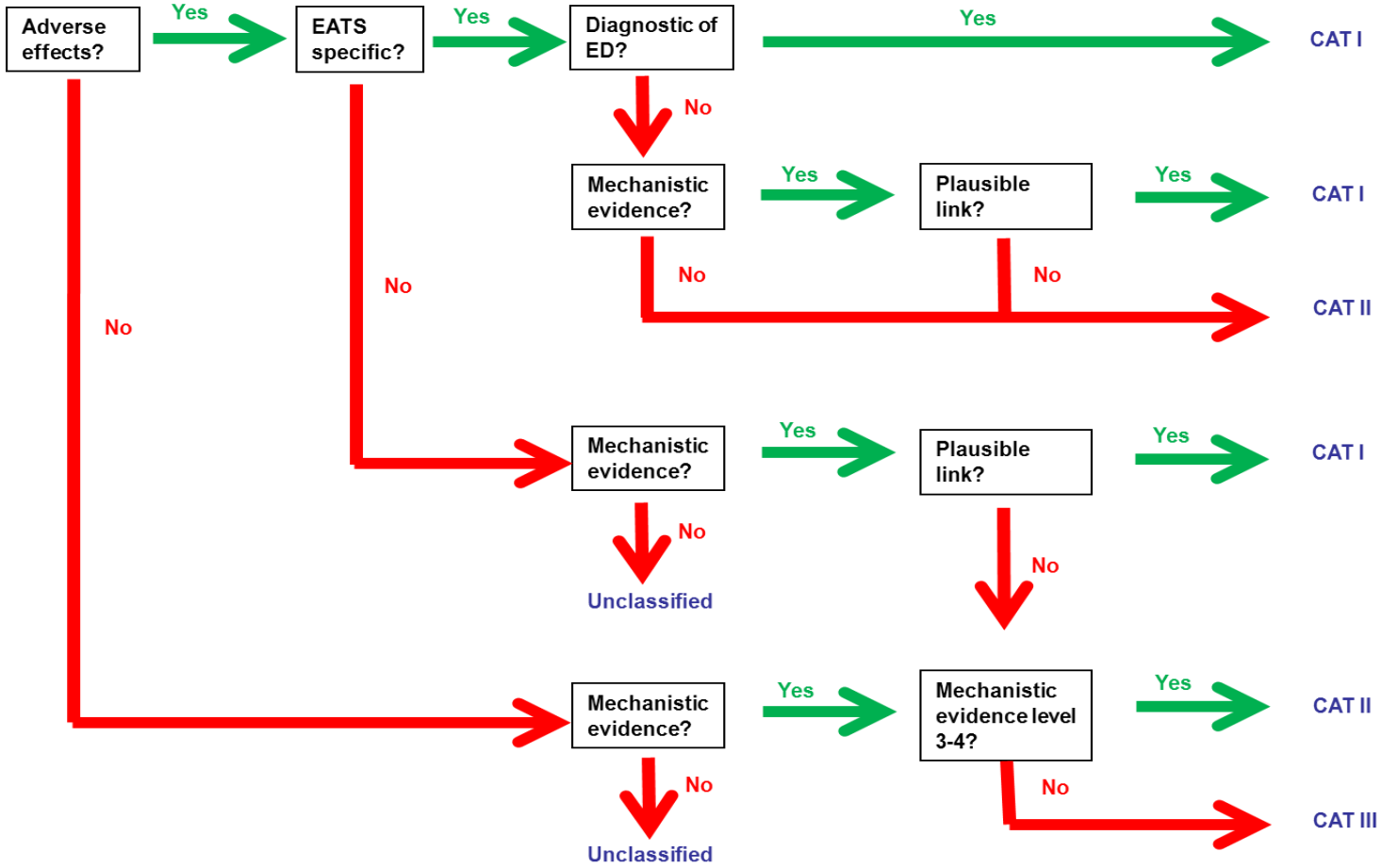
Data summary example

OECD CF level	Study	Species	Endocrine effect	Direction	NO(A)EL	Specific for
5	Mammalian 2-generation	Rat	Female fertility	Decrease	28.4	N
			Ovary weight	Decrease	28.4	EAS
	Chronic/carcinogenic studies	Rat	Uterus weight	Increase	16.75	EAS
4	No data					
3	No data					
2	OT_ERa_ERb_1440_agonist		Receptor activation	Increase		E
	OT_ERbERb_1440_agonist		Receptor activation	Increase		E

Practical implementation of methodology



Concluding Remarks

- Draft Screening Methodology submitted to contractor, includes:-
  - data sources to be consulted
  - type of data to extract
  - template for recording and summarising data
  - decision trees to follow to apply options for criteria in a systematic manner to 700 substances,

Concluding Remarks

- Contractor applying methodology to sample subset (35 substances) to test practical operability
- Fine tuning/adjustments according to feedback by end of June
- Methodology to be applied in a phased manner to PPPs, Biocides and selection from REACH, cosmetic ingredients and priority substances under water framework directive
- Many substances likely to be unclassified based on lack of mode of action data
- Distinguish between 4 options in roadmap
- Strike appropriate balance between resources, time constraints and depth of analysis

Thank you for your attention

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