IDENTIFICATION OF ENDOCRINE DISRUPTING PESTICIDES:

TRAPPED IN A VICIOUS CIRCLE

Summary

The current EU policy to test if a pesticide is an endocrine disruptor (altering the function of human and animal hormonal system) is far from being implemented. Endocrine disruption is a serious health concern that could lead to reproductive effects, cancer, brain damage and a range of other diseases. PAN Europe's survey on the approval decisions of 33 pesticide active substances in Europe revealed that in 31 cases no relevant testing -specific to assess endocrine disruption- was requested from industry. While OECD-tests are available and agreed since 2012, the most sensitive tests were never requested from industry and even the tests to just determine endocrine activity were requested only in very few cases (4 of the 33 decisions studied). Additionally, in 4 other cases where Food Authority EFSA advised requesting OECD-tests, the European Commission refused to oblige industry to do so, ultimately saving costs for industry. The EFSA/ECHA Guideline from 2018 on the identification of endocrine disrupting pesticides (EDPs)[1] is very clear on testing requirements and mentions on page 32 a range of OECD-tests that "need to be available" to decide on EDPs. Overall, Commission's testing policy is very inconsistent, but -most importantly- fails to oblige industry to do OECD-tests as prescribed by the 2018-Guideline on endocrine disruptors. Commission thus relies in the majority of the cases on the available old, outdated and non-ED sensitive animal testing data. EFSA, in several cases (the pesticides Dimethenamid, Pendimethalin), acknowledges that "sensitive endpoints" in the related industry studies are lacking, and still draws the conclusion "unlikely to be an EDP". However, without the correct data, EDPs will never be identified.

For about half of the cases surveyed by PAN Europe, DG SANTE only requested "information" (12 cases) or an "updated assessment" (in 4 more recent cases). The information for the 12 cases has to be provided only after a new approval period for the pesticide is granted. In 10 out of these 12 cases, industry didn't even submit the requested "information" at all, and the Rapporteur Member State in charge of the assessment accepted this. This clearly futile procedure puts the control of the identification process into the hands of the industry, allowing them to repeat claims that their pesticide is not an endocrine disrupting pesticide (EDP), and grants them another 10 years of market access. Many years of authorisation (approval) are added with a failing protection of the public.

Furthermore, many potential endocrine disrupting effects observed in animal studies are downplayed by EFSA and the Commission with views as "indirect effect" (Fluopyram), "only at high dose" (2,4-D, Flurochloridon, Trifloxystrobine), "likely other mechanisms" (Propyzamide), "non-treatment related" (Florpyrauxifen), "within historical control data range" (Flutianil), which are all speculations based on little experimental evidence. In the best cases, the assessment concludes that "endocrine effect couldn't be excluded" and "information is needed to confirm absence of ED-activity". It seems as if regulators do not try to identify EDPs but try to do their best to dismiss effects that could be related to endocrine disruption and consequently give the green light for the pesticide to remain on the market. Even the 7 pesticides out of the 33 surveyed by PAN Europe that were already identified as an

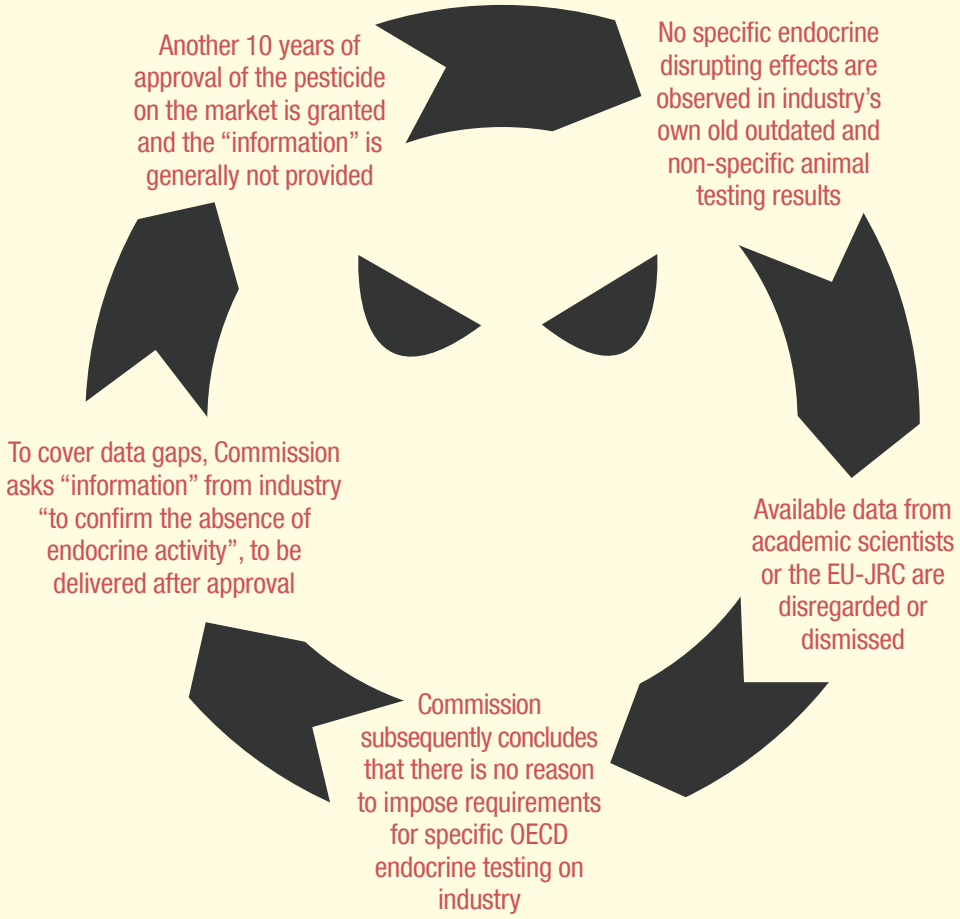
1. www.efsa.europa.eu/en/press/news/180607

EDP by EU-JRC (Joint Research Center, Ispra), were either dismissed by Commission from being EDPs (the pesticides Pendimethalin, Propyzamide, L-cyhalothrin), or approved for another 10 years with the futile request for additional "information" (the pesticides Epoxiconazole, Prochloraz, 2,4-D, Tetraconazole). This demonstrates the weakness of the safety assessment of pesticides and the random outcome of "expert judgement" (the opinions and feelings of those experts that happen to do the assessment).

Very disturbing is the fact that EFSA and the Commission apply the concept of "potency", that was found unfit for decision making and therefore was excluded from the scientific criteria in 2016. This is the case for the pesticides 2,4-D, Trifloxystrobin, Epoxiconazole and Flutianil. Effects were dismissed when they were above the NOAEL for a non-ED adverse effect.

Furthermore, the Pesticide Regulation is underpinned by the precationary principle to ensure that pesticides do not adversely affect human and animal health or the environment. Since in most of the cases examined, adverse effects were observed in animal studies following exposure to the active susbtance, simply guessing that these are not endocrine related without providing robust evidence, is against EU law and therefore should be considered illegal.

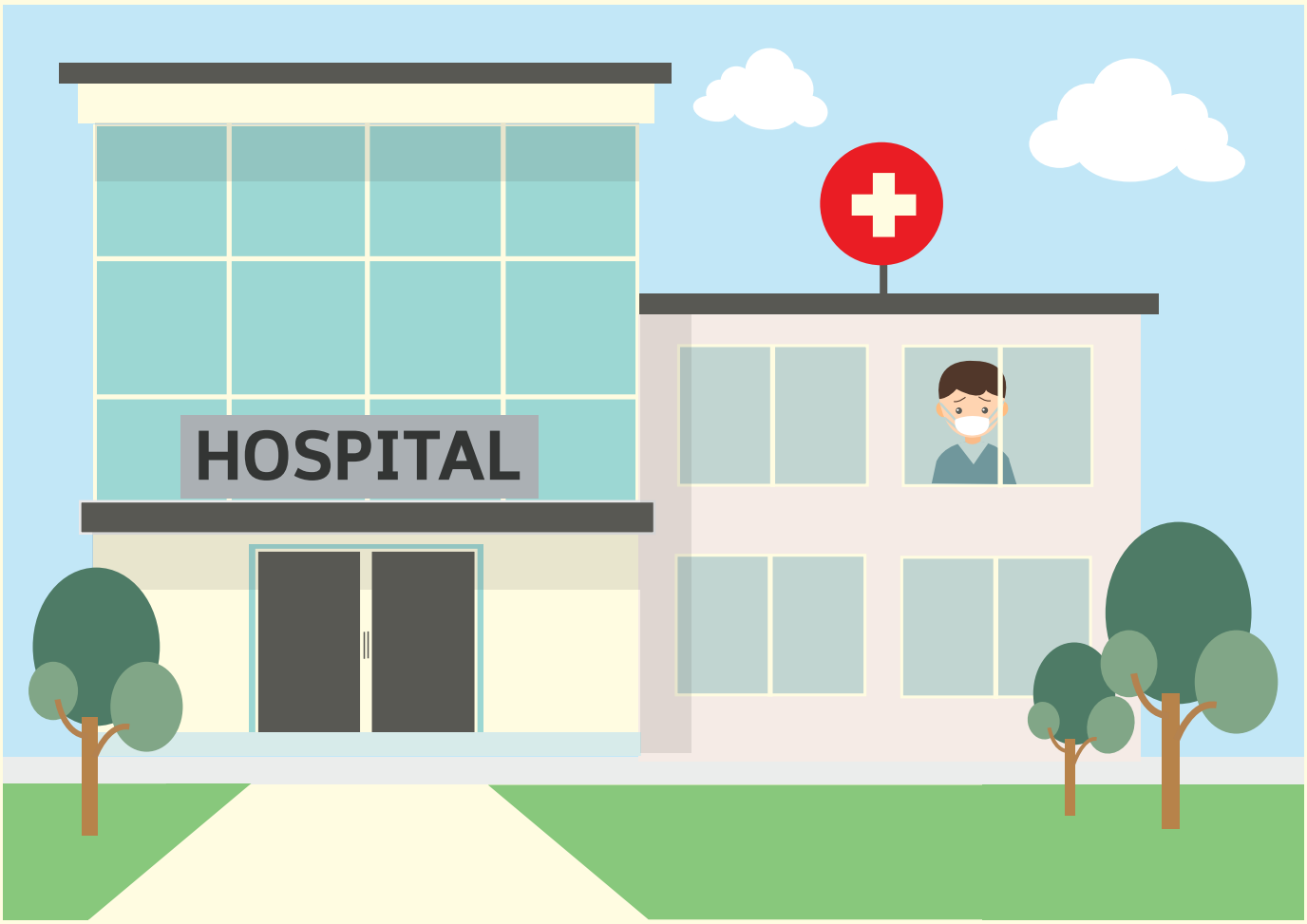
In conclusion, Commission's policy is effectively blocking the identification of endocrine disrupting pesticides and it very much looks like another loophole (a vicious circle) is put in the way by regulators to stop the policy on endocrine disruption. An obstruction that is ongoing now for more than 9 years[2 3].



2. www.pan-europe.info/resources/reports/2015/05/pan-europe-reconstruction-downfall-eu-endocrine-policy
3. www.eureporter.co/environment/2019/05/10/health-officials-protected-use-of-32-dangerous-pesticides/

Introduction

EU Parliament, Commission and Council decided to adopt an unique -first in the world- policy in 2009 by disallowing any exposure of the public to the dangerous group of endocrine disrupting pesticides. The Table next page[4] shows the type of adverse effects one might expect for these chemicals. It has been calculated that health effects from exposure to endocrine-disrupting chemicals cost the EU €157 billion each year, with pesticides being one of the main contributors to these costs[5].



4. https://publ ications.europa.eu/en/publication-detail/-/publication/6b464845-4833-11e8-be1d-01aa75ed71a1/language-en
5. Trasade at al 2016. Burden of disease and costs of exposure to endocrine disrupting chemicals in the European Union: an updated analysis

Overview of human diseases associated with endocrine disruption	
Adverse outcomes	**Specific outcomes**
Male Reproductive Health	Reduced semen quality and function
	Cryptorchidism
	Hypospadias
	Benign Prostatic Hyperplasia (BPH)
Male and Female Reproductive Health	Impotence for both sexes
Female reproductive Health	PCOS
	Uterine fibroids
	Endometriosis
	Precocious puberty
	Fecundity
	Adverse pregnancy outcomes
	Menopause-related
Hormone cancer	Female breast cancer
	Male breast cancer
	Prostate cancer
	Testis cancer
	Thyroid cancer
	Ovarian cancer
	Endometrial cancer
	Fallopian cancer
	Liver cancers (Steroid induced)
Metabolic dysfunction	Obesity
	Diabetes
	Metabolic syndrome
Neuro development	Hypothyroxinemia
	Autism
	ADHD
	Neural defects
	Cortisol Axis (potential)
	Mental Health
	Neurodegenerative Disease / Peripheral neuropathy
	Altered Stress Response
Immune, Autoimmune and Inflammatory disorders	Hashimoto
	Immune dysfunction
	Autoimmune
	Chronic inflammation
	Immune suppression
	Asthma
	Allergies
Retinoid Target Malformations	Craniofacial /cleft palate
Other	Cardiovascular disease
	Respiratory disease
	Osteoporosis
	Blood pressure
	Tachycardia

In 2009, EU Commission, Parliament and Member States, agreed to put endocrine disrupting pesticides at the same level of concern (hazard) as those classified as carcinogenic, reprotoxic and mutagenic (CMR pesticides) and ban them from the EU market. Humans, animals and the environment should not be exposed to any pesticide substance with hazardous properties, including endocrine disruptors and the exceptions are only minor. In case of uncertainty the precautionary principle must apply. Since that time an unprecendented lobby against this legal requirement has started by the pesticide industry, which is supported by US Embassy, several EU Commission services, Food Authority EFSA and its panels, and other pressure groups[6] [7] [8] [9] [10] [11] [12] [13] [14] [15]. Their objective has been to undermine democratically agreed rules on endocrine disrupting pesticides (EDPs) and change the "no exposure" rule (the "hazard"-based approach) back to traditional risk assessment that allows human and environmental exposure, leading to market approval of substances that are classified as hazardous. Due to internal "blockades"[16] (e.g. the Commission Secretary General removed DG Environment as the lead DG on the ED criteria), the EDP-policy was severely delayed and the criteria for the identification of EDPs surpassed the legal deadline of 2013 to get established 5 years later, in 2018[17]. A total destruction of the EDP-policy was successfully avoided due to pressure from the public, civil society organisations and the EU-Parliament[18]. Nevertheless, the criteria were still designed in such a way that it is still very hard to prove that a pesticide is an EDP. Three times more evidence is needed for identifying an EDP compared to the evidence needed to identify a carcinogenic pesticide (the observed adverse effect, the endocrine activity and the link between the two must be established)[20]. This again shows the reluctance of EU Commission to implement the rules. Now that the criteria are finally established, the Commission should start banning EDPs. However, data for identifying an EDP[19] are lacking from the application dossiers. This is unacceptable, especially because more data are now necessarily since the burden of proof has been set very high. That is why PAN Europe started this survey to find out how Commission generates data to identify EDPs and analysed 33 decisions of the past years to find out the policy applied by Commission.

6. *www.pan-europe.info/resources/reports/2015/05/pan-europe-reconstruction-downfall-eu-endocrine-policy*
7. *www.demorgen.be/nieuws/zwart-op-wit-bewezen-europa-buigt-voor-pesticidelobby~b9ae76fe/*
8. *www.theguardian.com/environment/2015/may/22/eu-dropped-pesticide-laws-due-to-us-pressure-over-ttip-documents-reveal*
9. *www.etui.org/Topics/Health-Safety-working-conditions/News-list/Senior-EU-officials-and-industry-lobbies-joined-forces-to-undermine-the-European-strategy-against-endocrine-disruptors*
10. *www.oneworld.nl/achtergrond/un-experts-industry-misleads-endocrine-disruptors/*
11. *https://theecologist.org/2019/apr/12/eu-may-legalise-human-harm-pesticides*
12. *www.eureporter.co/environment/2019/05/10/health-officials-protected-use-of-32-dangerous-pesticides/*
13. *www.efsa.europa.eu/en/press/news/130320*
14. *www.brusselstimes.com/all-news/eu-affairs/56506/documents-lobbies-attempts-cripple-undermine-pesticide-regulation-eu/*
15. *www.pan-europe.info/press-releases/2019/05/top-eu-officials-fought-higher-pesticide-exposure-secret-documents-show*
16. *www.pan-europe.info/press-releases/2015/05/eu-health-policy-endocrine-disruption-collatoral-damage-commission-health*
17. *https://ec.europa.eu/health/endocrine_disruptors/overview_en*
18. *www.pan-europe.info/press-releases/2017/10/commissions-endocrine-criteria-proposal-beyond-legal-mandate-eu-parliament-0*
19. *www.pan-europe.info/resources/briefings/2016/07/pan-europes-response-coms-edc-criteria-feedback-mechanism*
20. *For human health 3.6.5 Annex II to Reg 1107/2009 describes that a substance "shall be considered as having endocrine disrupting properties that may cause adverse effect in humans if, ... it is a substance that meets all of the following criteria, unless there is evidence demonstrating that the adverse effects identified are not relevant to humans: (1) it shows an adverse effect in an intact organism or its progeny, which is a change in the morphology, physiology, growth, development, reproduction or life span of an organism, system or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress or an increase in susceptibility to other influences; (2) it has an endocrine mode of action, i.e. it alters the function(s) of the endocrine system; (3) the adverse effect is a consequence of the endocrine mode of action." Similarly, 3.8.2 of Annex II refers to non target organism.*

Analysis

Table Index

Pesticide & classification:
Name of active substance and classification (if available)

Is ED evidence reported by industry (EFSA)?:
As observed in scientific opinion of Food Authority EFSA, Parma

Is ED evidence reported by industry (IA):
As observed by MS analysis (Benaki) -impact Assessment ED criteria- for JRC - 2016)

Is ED evidence reported in public literature?
PUBMED search and analysis

Commission's approval decision:
Date of Commission's conclusion on active substance

ED Testing requirements:
Data requirement according to Regulation (EC) 283/2013.
8.2.3. If there is evidence that the active substance may have endocrine disrupting properties, additional information or specific studies shall be required: — to elucidate the mode/mechanism of action, — to provide sufficient evidence for relevant adverse effects. Studies required shall be designed on an individual basis and taking into account Union or internationally agreed guidelines, in the light of the particular parameters to be investigated and the objectives to be achieved. 8.1.5: Consideration shall be given to whether the active substance is a potential endocrine disruptor according to Union or internationally agreed guidelines. This may be done in consulting the mammalian toxicology section (see Section 5). In addition, other available information on toxicity profile and mode of action shall be taken into account. If as a result of this assessment, the active substance is identified as a potential endocrine disruptor, the type and conditions of the study to be performed shall be discussed with the national competent authorities. 8.2.2.2: For active substances that fulfil the screening criteria on either of the fish screening assays, or for which there are other indications of endocrine disruption (see 8.2.3), appropriate additional endpoints shall be included in the test and discussed with the national competent authorities.

Confirmatory information for ED requested/submitted:
Regulation (EC) 1107/2009.
Art. 6f: submission of further confirmatory information to Member States, the Commission and the European Food Safety Authority, (the Authority), where new requirements are established during the evaluation process or as a result of new scientific and technical knowledge;

EFSA/ECHA Guideline:
Implementation of the EFSA/ECHA Guideline on the identification of EDCs, where according to Page 34; "Based on the current knowledge and available test guidelines, to consider the EATS-related endocrine activity sufficiently investigated with respect to humans and mammals (as non-target organisms), the information described below, needs to be available in order to support a conclusion on absence of EATS-related endocrine activity". These OECD TG for the so-called OECD level 2/3 test are 455, 440 , 229, 458, 441, 229, 456, 321.

PAN Europe observations regarding patterns in decision taking

Pesticide & classification	1. TETRACONAZOLE
Is ED evidence reported by industry (EFSA)?	With regard to the increased incidences of absent corpora lutea and squamous metaplasia (that were not seen in the two-generation reproduction study) the experts noted that it could not be excluded that they were caused by hormonal effects of tetraconazole in particular since other triazoles have been shown already to possess endocrine disrupting properties.
Is ED evidence reported by industry (IA)?	**YES, ED-adverse carc-effects**: *Absence of corpora lutea (rat, 104-week), *Changes in fetal development: extra ribs, hydroureter and hydronephrosis (rat), *Dystocia (rat), *Increased gestation length (rat), *Decreased litter/pup weight (rat), *Pup mortality (rat), *Increased adrenals weight (rat)is observed only in a 13-week study and not in longer duration studies, so it is disregarded due to low weight of evidence. **YES, ED-adverse repro-effects**: *Ovary histopathology: squamous metaplasia in endometrial glands (rat, 107-week), *Increased ovary weight (rat) is observed only in one 13-week study and not in longer duration studies, so it is disregarded due to low weight of evidence. **YES, ED-mechanistic info on carc**: *Aromatase inhibition (high potency), *AR binding (high potency), *AR coactivator recruitment (medium potency) *4 studies show no effect on AR receptor, *No effect Estrogen receptor: (from ToxCast prediction)* No effect Thyroid receptor
Is ED evidence reported in public literature?	
Commission's approval decision	January 2010
ED Testing requirements	The Member States concerned shall request: *….further information on the potential for endocrine disrupting effects to birds, mammals and fish.*
Confirmatory information for ED requested/submitted	Confirmatory data was submitted and evaluated. The amended renewal report of 2017 states that "it cannot be excluded that tetraconazole exhibits endocrine disrupting effects to mammals, birds and fish. Although extensive information has been provided, it is agreed that these matters could not be unequivocally assessed in the state of science existing at the time of the data submission. As a consequence, it will be necessary to reconsider the matter at renewal stage, on the basis of the pertinent regulatory criteria and the appropriate harmonised guidance that will then have become of application." Application for renewal received in December 2016. Dossier submission expected for 30 June 2019.
EFSA/ECHA Guideline	Nothing yet
PAN Europe observations regarding patterns in decision taking	Remarkable that no ED test for humans are requested; how is the environment (fish, birds) dealt with for ED? Apparently, the testing for birds etc. is not very helpful and/or easily evaded by industry (CD procedure); In the end the only effect observed is 10 years of delay. Industry will always submit information that concludes no ED-activity. So what is the point of asking information?

Pesticide & classification	**2. FLUROCHLORIDONE (resubmission)** One of the 32 of JRC/Benaki.
Is ED evidence reported by industry (EFSA)?	The target organs of FLC are the testis and epididymides in male rats, with dogs, mice, rabbits and monkeys being less sensitive to these effects. Increased incidence of abnormal sperm and decreased sperm count at higher dose levels are the outcome. Sertoli cell vacuolation was observed in rats. As Sertoli cells are involved in hormonal control of male reproductive functions, FLC could be considered as a potential endocrine disruptor.
Is ED evidence reported by industry (IA)?	**YES, ED-adverse carc:** Increased adrenals weight (mouse), Changes in fetal development: visceral malformations, skeletal malformations, skeletal variations (rat)], Decreased fetal weight (rat), Decreased number of implantations/corpora lutea (rat) Post implantation loss (rabbit)], Decreased reproduction (positive mating) (rat)], Decreased number of live births (possibly linked to low litter size and litter/pup weight) and increased pup mortality (rat) . **YES, ED-adverse eff repro:** Epididymis histopathology: tubular epithelial hyperplasia (rat), Increased ovary weight (rat), 4 (mouse)], Changes in sperm morphology: sperm degeneration, abnormal sperm (rat), Decreased sperm motility (rat), Decreased sperm numbers (rat), Testis histopathology: atrophy, Sertoli cells vacuolation (rat), Decreased testis weight (rat). **YES, toxic eff ED-organs:** Increased FSH (rat), Increased LH levels (rat), "Flurochloridone affects the seminiferous epithelial cycle of the testes (rat, rabbit, monkey) at the primary spermatocyte stage by acting on the Sertoli cells as indicated in the EFSA conclusion 2010." **YES, ED-link:** As indicated in the EFSA conclusion (2010), Flurochloridone affects the seminiferous epithelial cycle of the testes at the primary spermatocyte stage by acting on the Sertoli cells. As a result all the relevant EATS-specific adverse effects in testes, epididymis and sperm are observed. Furthermore, increased FSH levels could be linked to increased ovary weight.
Is ED evidence reported in public literature?	
Commission's approval decision	June 2011
ED Testing requirements	The Member States concerned shall ensure that the applicant submits to the Commission further confirmatory information as regards: …… 4. the potential endocrine disrupting properties of flurochloridone. The Member States concerned shall ensure that the applicant submits to the Commission ….. the information set out in point (4) within two years after the adoption of the OECD test guidelines on endocrine disruption.
Confirmatory information for ED requested/submitted	Application for renewal received in May 2018. Dossier submission expected for 30 November 2018
EFSA/ECHA Guideline	Nothing yet
PAN Europe observations regarding patterns in decision taking	This is one of the **32 pesticides identified as a full ED-pesticide** in the JRC imapct assessment (Benaki). Delegating to MS seems a futile procedure. Apparently nothing happened in these 10 years.

Pesticide & classification	3. DIFENOCONAZOLE (resubmission), CfS
Is ED evidence reported by industry (EFSA)?	During the peer-review process concerns were raised regarding the potential endocrine disrupting properties of difenoconazole (DMI-fungicide family). There were indications in open literature that difenoconazole is an aromatase inhibitor, but information from the toxicology section gave no indications of endocrine disruption. Therefore, the Member State experts at PRAPeR TC 42 agreed that concern for endocrine disruptive effects in birds and mammals was low. It was noted that the information on birds and mammals would not be appropriate to cover the potential endocrine disruption on fish.
Is ED evidence reported by industry (IA)?	**NO (all secondary):** The developmental and reproductive adverse effects are observed at maternal toxic dose levels; therefore these effects have been excluded from the evaluation / categorization procedure. Effects on adrenals and ovaries were observed only in study ID4 (90 days study), while no such effects were observed in chronic study (ID9, 1 1/2 year study) conducted in the same species (mouse). Adverse effects were observed only in study ID1 and ID7 (~ 30 days studiew]s), while no such effects were observed in chronic study (ID8, 2 years study) conducted in the same species (rat).
Is ED evidence reported in public literature?	Several studies (6) in fish showing endocrine disruption, activity, adverse effects (sperm, reproduction) and a link between the two
Commission's approval decision	Approved 2009, EFSA pr 2011
ED Testing requirements	The notifier shall submit confirmatory information as regards: .. (c) the potential for endocrine disrupting effects on fish (fish full life cycle study) and the chronic risk to earthworms from the active substance and the metabolite CGA 205375 (1); The notifier shall submit to the Member States, the Commission and the Authority the information set out in point ….. and (c) by 30 November 2013 …….
Confirmatory information for ED requested/submitted	There is an agreement among the RMS, EFSA and MSs (i.e. DE and DK, however see NL comment in 5(15)) that the submitted fish study does not provide sufficient evidence to conclude that there are no endocrine disruptive effects on fish. (EFSA public consultation on the confirmatory data submitted, 2014). Notes: Another study was available for the national product authorisation in Sweden. Although this study was not evaluated in detail, it was noted that there was a large variation of female vitellogenin levels among the tested fish and a low statistical power was anticipated. These findings are in line with the findings of the submitted study for the confirmatory dossier. Renewal process is ongoing. RAR from RMS to be expected mid 2018.
EFSA/ECHA Guideline	Only discussion on fish. Why nothing on mammals?
PAN Europe observations regarding patterns in decision taking	Again industry manages to submit information (sloppy studies) that is not very useful for drawing conclusions. Issue postponed to the moment the ED criteria are available. Again 10 years of delay.

Pesticide & classification	**4. EPOXICONAZOLE, C2, R1B, CfS, ED properties One of the 32 of JRC/Benaki.**
Is ED evidence reported by industry (EFSA)?	Results from new in vitro studies and a new developmental study in rats confirm that epoxiconazole has endocrine disrupting properties but do not merit changing relevant NOAELs or revising the proposed classification according to an evaluation by the rapporteur Member State. However, these new data have not been peer reviewed.
Is ED evidence reported by industry (IA)?	**YES, ED-adverse carc:** *Dystocia (rat), *Decreased fertility (rat), *Increased gestation length (rat), *Decreased lactation index (rat), *Decreased litter/pup weight (rat), *Decreased number of live births (rat), *Increased time to mating (rat), Vaginal haemorrhage (rat), *Post implantation loss(rabbit); (rat)] **(indicated due to change in estradiol level!),** *Resorptions (rabbit); D(rat)], *Ovarian theca granulosa cell tumours (rat), Adrenal gland cortex tumours (rat), *Changes in fetal development: skeletal variations (rudimentary cervical and/or accessory 14th ribs); cleft palate; absent or small tuberositas deltoidea (rat), *Increased placental weight (rat) and placental histopathology, Decreased fetal weight (rat]; Increased fetal weight (rat),] *Increase fetal mortality [ID: 45] and litter size, *Decreased number of live births (rat), *Pup mortality (rat), *Decreased number of live fetuses (rat), *Decreased adrenals weight (rat): This effect is disregarded since it is not reproduced in longer duration studies. *Increased adrenals weight in guinea pig are not accompanied by any other ED-related or EATS specific effects, so the effects is disregarded due to low weight of evidence. **YES, ED-adverse repro:** *Increased anogenital distance in rat: observed in fetuses of both sexes and in newborn female but not male offsprings, *Increased estrus cyclicity (rat), *Ovary histopathology: deposistion of amyloid (mouse), *Ovary histopathology: ovarian cysts (rat), *Testis histopathology: deposition of amyloid (mouse), Epididymis histopathology and weight (decrease), *Decrease in sperm numbers and motility, *Decrease in age of vaginal opening and testis descent (rat), *Decrease in uterus weight (guinea pig). **YES, mechanistic info:** *Decreased estradiol levels (rat), *Increased FSH levels (rat), *Increased testosterone levels (rat), *Increase testosterone level (guinee pig) **YES, ED-link:** Decreased estradiol levels accompanied by increased testosterone levels indicate an inhibition of aromatase activity, as indicated by all the available in vitro studies. This alteration of steroidogenesis may be responsible for the adverse effects observed i.e. increased anogenital distace in females, increased estrus cyclicity, increased time to mating, decreased fertility and increased fetal weight (an increased fetal weight might be related to the up-regulated levels of testosterone observed in the dams; Taxvig et al., 2008).
Is ED evidence reported in public literature?	Dresing 2013 on 5 conazoles: Ketoconazole and epoxiconazole are the most potent embryotoxic compounds, whereas prochloraz belongs to the most potent developmental toxicants. Also Castro 2012, epoxi developm tox. Greim Sharpe and others help industry by declaring epoxi is safe, (MOE)
Commission's approval decision	May 2009
ED Testing requirements	The Member States concerned shall ensure that the notifier submits to the Commission further studies addressing the potential endocrine disrupting properties of epoxiconazole within two years after the adoption of the OECD test guidelines on endocrine disruption or, alternatively, of Community agreed test guidelines.
Confirmatory information for ED requested/submitted	Confirmatory data requirement was set 'within 2 years after the adoption of OECD or Community test guidelines'. The applicant provided some information to address (at least part of) the requirment. Inconclusive on ED. (CD procedure was done while classification R1B was ignored!) Renewal process is ongoing. RAR expected from the RMS end 2018
EFSA/ECHA Guideline	Now two years after adoption of the OECD test, but in reality no OECD tests provided..
PAN Europe observations regarding patterns in decision taking	Delegating to MS seems a futile procedure. Apparently nothing happened in these 10 years. Remarkable for a pesticide with such a high amount of evidence for ED. Even at CD review, R1B classification ignored! **Full ED acc. to Benaki** (adverse + mechanistic +link), still no action. Epoxiconazole powerful ED embryotoxic toxin. Epoxiconazole is a CfS due to ED-properties

Pesticide & classification	5. FLUQUINCONAZOLE, Resubmission
Is ED evidence reported by industry (EFSA)?	
Is ED evidence reported by industry (IA)?	
Is ED evidence reported in public literature?	
Commission's approval decision	January 2012
ED Testing requirements	The applicant shall submit confirmatory information as regards: ….. (6) the endocrine disruption potential in aquatic organisms (fish full life cycle study). The applicant shall submit to the Commission, the Member States and the Authority such information by 31 December 2013.
Confirmatory information for ED requested/submitted	IE (former RMS) analysed the information submitted and considered that the substance is not ED. Deadline for application for renewal of approval 31 December 2018. Deadline for submission of dossier: 30 June 2022.
EFSA/ECHA Guideline	Only discussion on fish.
PAN Europe observations regarding patterns in decision taking	

Pesticide & classification	6. ACIBENZOLAR-S-METHYL (BENZOTHIADIAZOLE), (EFSA tbc R2)
Is ED evidence reported by industry (EFSA)?	EFSA (2014) proposes classification as toxic for reproduction category 2, and effects that may be linked to endocrine organs, resulting in impaired development of the cerebellum. Data gap for the OECD level 2/3 tests is relevant for the interpretation of the interim criteria
Is ED evidence reported by industry (IA)?	No information
Is ED evidence reported in public literature?	
Commission's approval decision	April 2016: No specific indication is available that the morphometric changes in the cerebellum of foetuses are determined via one of the EATS (oestrogen, androgen, steroidogenesis and thyroid) axis. Therefore no specific OECD validated test methods could be requested at this stage. Moreover, US EPA ToxCastTM data, (available post dossier submission) indicate no evidence for an endocrine mediated mode of action of acibenzolar-S-methyl.
ED Testing requirements	Irrespectively from the endocrine disrupting potential of acibenzolar-S-methyl, confirmatory data are requested to investigate further on the relevance and reproducibility of the morphometric changes observed in the cerebellum of foetuses in a developmental neurotoxicity study.
Confirmatory information for ED requested/submitted	No Data submitted. Evaluation ongoing by RMS FR.
EFSA/ECHA Guideline	Moved away from ED-qactivity (without experimental evidence)
PAN Europe observations regarding patterns in decision taking	**Commission** only looks at EATS axis and ignores all other endocrine disrupting options. **Commission** ignores the interim criteria (and EFSA opinion). If no information is available for a link with the EATS axis, **Commission** will not oblige any endocrine testing (precautionary principle?), even while EFSA indicated level 2/'3 test are necessary **Commission** takes US EDSP outcome for granted (while the use of MOE is not EU policy). What about US Toxcast? Is this reliable and acceptable in EU context?

Pesticide & classification	**7. PROCHLORAZ (CONAZOLE), Resubmission One of the 32 of JRC/Benaki.**
Is ED evidence reported by industry (EFSA)?	Effects on ovaries, prostate and thyroid could be due to endocrine disruption (DAR 2007, CRD); Specific in vivo tests for endocrine disruption suggest that endocrine disruption is having an effect on reproductive systems and thyroid hormones (case study OECD); ED-mechanism (oestrogen and androgen antagonism and disruption of steroidogenesis) in-vivo effects on the reproduction systems and the thyroid (effects on T4 and TSH) (inde lit);
Is ED evidence reported by industry (IA)?	**YES, ED-adverse eff carc:** Dystocia (rat), Increased gestation length (rat), Decreased litter size (rat), Decreased number of live fetuses (rat), Decreased number of implantations/corpora lutea (rat), Resorptions (rabbit), **YES, ED-adverse repro:** *Decreased prostate weight in mouse and dog and increased prostate weight in rat are not taken into consideration for the evaluation due to no reproducibility in longer duration studies.Decrease Seminal vesicles weight: (rat), Epididymis weight: ID 9 in rat increase while ID 67a in rat decrease, Increase Age at preputial separation: (rat), Decrease Ano-Genital distance: (rat), Increase genitalia malformations: (rat), Decrease LABC weight: (rat), increase number of nipples in males:(rat), Changes of protein involved in steroidogenesis in male testicular fetus: in rat i.e. decreased testosterone levels. **YES, ED-mechanistic:** Testosterone level: 2 studies decrease (rat) 1 change (rat) and 1 no effect (rat). , Decrease LH level: (all rat), – Decrease T3/T4 level: (rat), Estradiol level: decrease and no effect (all rat), Decrease Glans penis weight (Hershberger): (rat), Decrease LABC weight (Hershberger):(rat), Decrease Seminal vesicles weight (Hershberger): (rat). **YES, ED-link:** A plausible link can be established considering the information in vivo mechanistic and EATS-adversity available mainly from studies ID 67a, 67b, 68 and 73a. Furthermore the plausible link can also be established with in vitro data. There is a clear pattern of EATS-specific effects demonstrating anti-androgenic activity adequately supported by in vivo and in vitro mechanistic data.
Is ED evidence reported in public literature?	Strong ED properties in at least a dozen independent studies
Commission's approval decision	January 2012
ED Testing requirements	The applicants shall submit confirmatory information as regards: ….. (3) the potential endocrine disrupting properties of prochloraz on birds. The notifier shall submit to the Commission, the Member States and the Authority the information set out in ….. point 3 within 2 years after the adoption
Confirmatory information for ED requested/submitted	Confirmatory data requirement was set 'within 2 years after the adoption of OECD or Community guidelines' No data submitted thus far. Deadline for application for renewal of approval 31 December 2018 Dossier submission is due on 30 June 2021
EFSA/ECHA Guideline	Another empty rule on delivering two-yaesr after OECD adoption. Nothing happend.
PAN Europe observations regarding patterns in decision taking	No endocrine testing for effects on humans (only birds) Data for birds apparently are not provided (waiting for community guidelines?) Confirmatory procedure futile **Full ED acc. to Benaki** (adverse + mehcanistic + link) Prochloraz powerful ED developmenatl toxicant.

Pesticide & classification	8. BENTAZON
Is ED evidence reported by industry (EFSA)?	Yes, EFSA 2015-opinion: Endocrine disrupting properties can be inferred from the observation of adverse effects on thyroid in mammals and birds. IC "not finalised". Data gaps: A data gap for the Level 2/3 tests currently indicated in the OECD Conceptual Framework was identified. The RMS disagrees with the data gap, considering unlikely that the increased post implantation loss, reduced number of foetuses and retarded foetal development are caused by an endocrine mediated effect.
Is ED evidence reported by industry (IA)?	**Yes: ED-related carcinogenic effects:** Retarded fetal development in the absence of maternal toxicity ; Reduced body weight in rat in the absence of maternal toxicity; Post implantation loss in rabbits, equivocal and in presence of maternal toxicity (reduced food consumption). However Benatzone is classified as Repr 2 H361d. Increased resorptions in rat.
Is ED evidence reported in public literature?	
Commission's approval decision	Approved for 7 years in 2018 (COM intended to approve only for non-food; MS resistance).
ED Testing requirements	The applicant shall submit by 1 February 2019 to the Commission, the Member States and the Authority confirmatory information as regards Level 2/3 tests as currently indicated in the OECD Conceptual Framework investigating the potential for endocrine-mediated effects of bentazone (to address the potential for endocrine-mediated mode of action regarding the developmental effects observed in a developmental toxicity study in rats (increased post implantation loss, reduced number of live foetuses and retarded foetal development in the absence of clear maternal toxicity suggesting that classification as reprotoxic category 2 may be appropriate)
Confirmatory information for ED requested/submitted	Yes
EFSA/ECHA Guideline	Yes. OECD toolbox applied
PAN Europe observations regarding patterns in decision taking	First time obligation level 2/3 tests (?) 2018

Pesticide & classification	9.THIFENSULFURON
Is ED evidence reported by industry (EFSA)?	EFSA peer-review, 2015: An endocrine-mediated mode of action regarding the occurrence of mammary gland tumours observed in the long-term toxicity study in rats cannot be excluded
Is ED evidence reported by industry (IA)?	**YES, ED-adverse carc:** Mammalian: Decreased absolute and relative adrenals weight (dog 90 days), Anomalies in renal papilla and delayed ossification-basis for the proposed classification [rat] **YES, ED-mechanistic:** Estrogen receptor and estrogen related receptor (trans) activation (medium and high potency)
Is ED evidence reported in public literature?	
Commission's approval decision	2016 approval with CI.
ED Testing requirements	The applicant shall submit to the Commission, the Member States and the Authority confirmatory information as regards: mechanistic data to rule out an endocrine mediated mode of action for mammary gland tumours; The applicant shall submit the information requested) by 30 June 2017
Confirmatory information for ED requested/submitted	
EFSA/ECHA Guideline	Only "information"
PAN Europe observations regarding patterns in decision taking	COM askes for data, industry delivers information

Pesticide & classification	**10. FLUTIANIL (approved) - EFSA tbc R2 and C2 (former IC), RAC: no classification.**
Is ED evidence reported by industry (EFSA)?	EFSA concluded R2 + C2 in the peer review back in 2014 (interim criteria) ; a data gap has been identified for the Level 2 tests currently indicated in the OECD Conceptual Framework. In the RAC committee the R2 and C2 were lifted based on new data sets on Historical Control Data Adverse effects have been observed on endocrine organs in different species and timelines (seminiferous tubules atrophy, testes softening and atrophy in mice, seminiferous tubules atrophy and cellular infiltrate of prostate in dogs, reduced number of implantation sites and pups delivered, increased histopathological findings and increased uterus weight, decreased ovary weight and atrophy, and carcinogenic effect on the pancreatic islet system in rats).
Is ED evidence reported by industry (IA)?	No information
Is ED evidence reported in public literature?	
Commission's approval decision	2019 approval March 2019, no endocrine
ED Testing requirements	As regards the new criteria to identify endocrine disrupting properties set in Commission Regulation (EU) 2018/605 (7), which became applicable on 10 November 2018, and the Joint guidance document to identify endocrine disrupting substances (8), the information contained in the conclusions of the Authority allow to infer that it is highly unlikely that flutianil is an endocrine disruptor via the estrogenic, androgenic, thyroidogenic and steroidogenic modalities. Although effects on the thyroid (weight increase) were observed, these occurred only at the top doses exceeding the maximum recommended doses for the type of study where the effects were observed. Testicular, prostate and uterus effects observed (histopathological changes) were within the historical control values or they were not replicated in the two-generation reproductive toxicity study, nor affected fertility parameters. The two-generation reproductive toxicity study was performed following the test protocol according to the latest OECD Guidelines (9), as prescribed by the Joint guidance document to identify endocrine disrupting substances and did not detect any endocrine sensitive reproductive and developmental parameters such as oestrous cycle length, mating index, mean number of implantation sites, preputial separation and vaginal opening.
Confirmatory information for ED requested/submitted	Yes, an updated assessment of the information submitted and, where relevant further information, confirming that flutianil is not an endocrine disruptor in accordance with Points 3.6.5 and 3.8.2 of Annex II of Regulation (EC) No 1107/2009
EFSA/ECHA Guideline	Despite questionable outcome (thyroid, prostrate effects, increasing control values, etc.) chronic animal studies were used, not the OECD toolbox
PAN Europe observations regarding patterns in decision taking	**Potency used for ED identification!!!!** In case of doubt (such as "not replicated"), DG SANTE concludes to NO endocrine! Further endocrine adverse effects dismissed with HCD!! In the end only "**information**" to "**confirm**" that it is no endocrine

Pesticide & classification	11. ISOXAFLUTOLE, R2, EFSA tbc C2. Former IC.
Is ED evidence reported by industry (EFSA)?	Considering the harmonised classification of isoxaflutole for Reproductive toxicity Category 2 and the proposed classification by the EFSA peer review as Carcinogen Category 2 a critical area of concern was identified with regard to Annex II, Point 3.6.5 of Regulation (EC) No 1107/2009. According to the current state of scientific knowledge, evidence of clear endocrine disrupting potential was not identified from the available studies and additional studies were not considered necessary (see Section 2).
Is ED evidence reported by industry (IA)?	No information
Is ED evidence reported in public literature?	
Commission's approval decision	Approval, May 2019, discussion in ScoPAFF, COM moved from non-approval to approval, because of IC (and risk for mammals) Bayer already applied for the two derogations (NE + 4.7) Reluctance in ScoPAFF on IC because the applicant didn't put forward information on ED.
ED Testing requirements	2019 approval, only information needed to 'confirm' that it is not an endocrine
Confirmatory information for ED requested/submitted	Yes, The applicant shall also provide an updated assessment to confirm that isoxaflutole is not an endocrine disruptor within the meaning of points 3.6.5 and 3.8.2 of Annex II to Regulation (EC) No 1107/2009,
EFSA/ECHA Guideline	Default position is that pesticide is safe, no OECD toolbox
PAN Europe observations regarding patterns in decision taking	One of the controversial IC-pesticides. Reg 1107/2009 orders a ban because of the IC but ScoPAFF blocks this because there is no ED effects demonstrated.

Pesticide & classification	12. AMISULBROM
Is ED evidence reported by industry (EFSA)?	As regards the potential for endocrine effects, the concern was raised because of an effect observed in the mammalian toxicology studies which caused a delay in reaching sexual maturation and decreased fertility; and because amisulbrom and metabolite IT-4 contained a triazole component. However, it was acknowledged that potential endocrine effects for wild mammals were considered covered by the reproductive endpoint, while the available studies were not sufficient to fully address this concern for birds and fish. It was recognised that the testing strategy for these types of assessments is still under development.
Is ED evidence reported by industry (IA)?	**NO ('secondary'), CLH Report 2014:** Decreased ovary and/or uterus weight in rat is considered a secondary consequence of impaired nutrition and growth. Sufficient mechanistic data and supporting evidence from the literature to conclude that the effects on fertility are the secondary consequence of impaired nutrition and growth during the early phase of development of the ovaries during the early phase of development of the ovaries and do not arise from a specific action of amisulbrom on fertility. Impaired fertility, delayed sexual maturation and reduced pup weight are considered secondary effects due to maternal toxicity and reduced bodyweight.
Is ED evidence reported in public literature?	
Commission's approval decision	July 2014
ED Testing requirements	The applicant shall submit confirmatory information as regards: …. (5) the potential for causing endocrine disrupting effects in birds and fish by amisulbrom and its metabolite 3-bromo-6-fluoro-2-methyl-1-(1H-1,2,4- triazol-3-ylsulfonyl)-1H-indole. The applicant shall submit to the Commission, the Member States and the Authority the relevant information set out …. under point (5) within two years after the adoption of pertinent OECD test guidelines on endocrine disruption.
Confirmatory information for ED requested/submitted	Technical report on the evaluation of the confirmatory data is available. All non-ED points are addressed and ok. For ED: The information provided for addressing the potential for causing endocrine disrupting effects in birds and fish by amisulbrom and its metabolite 3-bromo-6-fluoro-2-methyl-1-(1H-1,2,4-triazol-3-ylsulfonyl)-1H-indole(point (5)) should be complemented by further investigation of endocrine activity in order to draw a firm conclusion. Deadline for application for renewal of approval 30 June 2021 Dossier submission is due on 30 December 2021
EFSA/ECHA Guideline	Only birds and fish
PAN Europe observations regarding patterns in decision taking	Dismissing effects because they are 'secundary'is one of the most practiced RA decisions at EFSA (expert review would be useful). Still mid 2014 no ED-tests for humans requested

Pesticide & classification	13. MESOTRIONE, (EFSA tbc R2 and IC: toxic for endocrine organs)
Is ED evidence reported by industry (EFSA)?	Mesotrione is proposed to be classified as Repr. 2 for development by the peer review (in contrast with the harmonised classification according to CLP Regulation) and adverse effects were observed on endocrine organs. Therefore, according to the interim provisions of Annex II, point 3.6.5 of Regulation (EC) No 1107/2009 concerning human health, mesotrione may be considered to have endocrine disrupting properties. As no study is available to investigate a potential ED mode of action, a general data gap has been identified such as level 2 and 3 indicated in the OECD Conceptual Framework to address this issue;
Is ED evidence reported by industry (IA)?	**YES, ED-adverse carc:** Slightly increased abortion rates and skeletal findings indicative of delayed ossification (rabbit), Skeletal findings indicative of reduced or delayed ossification (rat and mouse), Reduced litter size, total litter weight and incresed incidences of whole litter loss, increased pup mortality (rat), reduced pup weight (mouse).
Is ED evidence reported in public literature?	
Commission's approval decision	June 2017
ED Testing requirements	The applicant shall submit confirmatory information as regards: ….. 2. the potential endocrine disrupting mode of action of the active substance in particular level 2 and 3 tests, currently indicated in the OECD Conceptual framework (OECD 2012) and analysed in the EFSA Scientific opinion on the hazard assessment of endocrine disruptors; The applicant shall submit to the Commission, the Member States and the Authority …. the relevant information requested under point 2 by 31 December 2017.
Confirmatory information for ED requested/submitted	Applicant has submitted info on ED. RMS completed their assessment. EFSA published an "outcome of the consultation" in Dec 2018: There was no overall consensus within the peer review to conclude on the endocrine disrupting properties of mesotrione, although there was a general agreement with the RMS assessment that the testis and epididymides findings reported in the multigeneration study should be considered unrelated to mesotrione administration. It is therefore proposed to further discuss the endocrine disrupting properties of the active substance in an experts' consultation. Syngenta submitted only level 2 studies and apparently the RMS (UK) agreed to this
EFSA/ECHA Guideline	Yes, OECD level 2/3 requested. Not fully submitted.
PAN Europe observations regarding patterns in decision taking	Another case of disregarding the Interim Criteria (IC) and bypass banning. In stead level 2/3 are requested (for what reason?). Why is EFSA suddenly involved (peer review CI)?

Pesticide & classification	**14. PENDIMETHALIN (EFSA tbc R2), CfS: Two PBT One of the 32 of JRC/Benaki.**
Is ED evidence reported by industry (EFSA)?	Based on indications of estrogenic and anti-androgenic activity in receptor binding and transcriptional activity assays in vitro, pendimethalin is an endocrine active substance. An increased uterus weight reported in a published study was not confirmed in the 2-generation reproductive toxicity study; however it is noted that the latter study was performed according to 1981 guidelines and may have missed sensitive parameters to endocrine disruption; sperm and sexual maturation parameters were not investigated, and oestrous cyclicity was only reported during mating. Thyroid effects were concluded to be primarily due to increased hepatic clearance of thyroid hormones. As there was no evidence for endocrine-mediated adverse effects in reproductive studies, it was considered that further data, such as the ones referred in levels 2/3 of the OECD Conceptual Framework for evaluating chemicals for endocrine disruption (OECD, 2012) would not add meaningful information regarding ED properties of pendimethalin according to current standards (EFSA Scientific Committee, 2013).
Is ED evidence reported by industry (IA)?	**YES, ED-adverse repro:** Thyroid histopathology findings, (rat), rat), (rat), (rat), (rat), Increased thyroid weight, (rat), (mouse), (rat), (rat), (rat). **YES, Toxic for ED-organs:** Decreased T3 levels, (rat), rat), (rat), (rat) ,rat), Decreased T4 levels, (rat), (rat), (rat), (rat), (rat), (rat), Increased TSH levels, (rat), (rat), (rat), (rat), (rat), (rat), (rat), Increased uterus weight (UT assay), (rat), Androgen receptor (AR) mRNA showed a marked down-regulation and ER-beta mRNA was up-regulated, (rat). **YES, ED-link:** The available in vivo mechanistic data (i.e. decreased T4 and T3 levels and increased TSH levels) are in concordance with the observed thyroid effects (increased thyroid weight, thyroid hypertrophy and hyperplasia)
Is ED evidence reported in public literature?	
Commission's approval decision	June 2017
ED Testing requirements	No mentioning of ED-activity
Confirmatory information for ED requested/submitted	No
EFSA/ECHA Guideline	Even EFSA not asking level 2/3
PAN Europe observations regarding patterns in decision taking	Clear ED activity and many missing information, still no obligations for ED-testing because of lacking adverse effects in reprotox studies (EFSA). Benaki even demonstrates adverse effects, toxicity for organs and a potential link. **One of the 32 of JRC !!**

Pesticide & classification	15. BROMOXYNIL R2 (EFSA tbc R1B, ED properties)
Is ED evidence reported by industry (EFSA)?	With regard to the scientific risk assessment, the experts agreed that thyroid toxicity in Fischer F344 rats might be endocrine mediated. Mechanistic information from the public domain also indicated potential mode of action of thyroid toxicity of bromoxynil. No evidence of thyroid toxicity in other studies/species and in other rat strains was observed. The experts proposed a data gap for further investigations of the potential endocrine-mediated properties of bromoxynil concerning thyroid toxicity.
Is ED evidence reported by industry (IA)?	**YES, ED-adverse carc:** Abortions,(rat), Decreased adrenal weights, (rabbit) (the only available Subchronic dermal toxicity), Fetal development alterations, (rat), (rat), (rat), (rabbit), (rat), (rat), (mouse), (rat), (rat), Decreased fetal weight, (rat), (rat), (rat), (rat) Decreased pup weight, (rat), (rat), Decreased pituitary weight, (rat), Increased post-implantation loss, (rat), Pup development alterations, (rat) **YES, ED-adverse repro:** Ovary histopathology findings, (rat), Uterus histopathology findings, rat), (rat), (rat). **YES, ED-mechanistic:** Transactivation antagonist (medium potency), No effects on estrogen receptor, IDs: 28, 30, 31, 35, 37, 39, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52 (IDs with no effects on transactivation: 30, 31, 49, 52), No strong evidence for ER (trans)activation, Also: Bromoxynil was found to be an efficient competitor for the T4 binding site of TTR (Transthyretin),
Is ED evidence reported in public literature?	
Commission's approval decision	Delay renewal because of derogation procedures (NE, 4.7) - four years already
ED Testing requirements	2019, discussion on derogations overrules endocrine debate
Confirmatory information for ED requested/submitted	
EFSA/ECHA Guideline	
PAN Europe observations regarding patterns in decision taking	Example of classified pesticide (R1B) that is kept unnecessary on the market with derogation procedures for 4 years unrestricted (PP?).

Pesticide & classification	16. FLUOPYRAM
Is ED evidence reported by industry (EFSA)?	Potential endocrine disruptor effects in birds and fish were discussed at the Pesticides Peer Review Meeting 94. It was noted that endocrine disruption effects could not be excluded with the available data. Therefore a data gap was identified to further address this issue for birds and fish. No direct endocrine disrupting effects were evident in mammals. It was agreed that indirect effects observed on the endocrine system were not of concern for wild mammals because they occurred at higher doses than the endpoint used for risk assessment.
Is ED evidence reported by industry (IA)?	**YES, ED-adverse carc:** Increased Adrenals weight (mouse), Adrenals histopathology: minimal to slight cortical vacuolation in female mice. **NO (secundary):** *Changes in fetal development in rat (visceral and skeletal minor variations) and decreased fetal weight are observed at the top dose, in presence of maternal toxicity, *Age at preputial separation and decreased litter/ pup weight (rat) are considered by RAC (2014) secondary effects to maternal toxicity, Effects on thyroid weight, thyroid histopathology in rat and mouse as well as thyroid tumors in male mice are due to liver enzyme induction, which is a CAR mediated MoA. This mechanism is not considered to be an ED-mediated mechanism. Therefore, these effects have not been considered for the evaluation as not informative to conclude on ED (RAC 2014). * Decreased fetal weight (rabbit) at maternal toxic dose
Is ED evidence reported in public literature?	
Commission's approval decision	February 2014
ED Testing requirements	The applicant shall submit confirmatory information as regards: (1) the long-term risk to insectivorous birds; (2) the potential for causing endocrine disrupting effects in non-target vertebrates other than mammals. The applicant shall submit to the Commission, Member States and the Authority the information set out in point 1 by 1 February 2016 and the information set out in point 2 within two years after adoption of the corresponding OECD test guidelines on endocrine disruption.
Confirmatory information for ED requested/submitted	Technical Report on the evaluation of the confirmatory data is available (Dec 2017) concluded that the refined risk assessment results in an acceptable risk for insectivorous birds on vines. However, the confirmatory data were not sufficient to resolve the high risk previously identified to birds for the uses in strawberries and tomatoes. No data were provided to address the potential for causing endocrine disrupting effects in non-target vertebrates other than mammals. No specific data submitted but in the comments on the assessments, EFSA and FR stated that some tests could have been performed to address ED. The applicant considered existing data showed lack of ED potential. Deadline for application for renewal of approval 31 January 2012 Dossier submission is due on 31 July 2021
EFSA/ECHA Guideline	Applicant considers existing data sufficient and refuses to do new tests
PAN Europe observations regarding patterns in decision taking	Sounds like applicants do not much effort on testing and just supply some old studies available. The word "endocrine" is missing in the chapter on mammalian toxicity (only regarding fish and birds). Sooooo many effects are qualified 'secundary"; what is the evidence?

Pesticide & classification	17. IPCONAZOLE
Is ED evidence reported by industry (EFSA)?	Furthermore, additional data gaps were identified at the meeting of experts to address further uncertainties associated with the available risk assessments for birds and mammals, including a data gap for potential endocrine mediated effects in birds.
Is ED evidence reported by industry (IA)?	**YES, ED-adverse carc:** "fatty" vacuolation in the adrenal cortex in dogs, Justification: As indicated in the DAR: Ipconazole, which like other triazoles, acts as a pesticide by inhibiting ergosterol biosynthesis in fungi, has been shown to reduce plasma levels of cholesterol in dogs. There is therefore a potential to affect steroid hormone levels. No hormonal measurements have been conducted in the submitted dog studies. However increased cortical "fatty" vacuolation of the adrenals is consistent with ipconazole having an effect on steroid hormone synthesis by the adrenal gland. It is also notable that there was no effect on leucocyte numbers in peripheral blood that would suggest a widespread inflammatory response. This is further supported by Everds et al.,2012 where degenerative changes of the adrenal cortex are often characterised by cellular vacuolation due to disruption of steroidogenesis. Increased adrenals weight & enlarged adrenals (cortical hypertrophy) in rats - consistent with the dog findings, WoE. **YES, ED-adverse repro:** Uterus and cervix weight decrease in rats - probably related to the decreased cholesterol levels and consistent with ipconazole having an effect on steroid hormone synthesis previously described.
Is ED evidence reported in public literature?	
Commission's approval decision	Sep-14
ED Testing requirements	The applicant shall submit confirmatory information as regards: (a) the acceptability of the long-term risk to granivorous birds; (b) the acceptability of the risk to soil macro-organisms; (c) the risk of enantio-selective metabolisation or degradation; (d) the potential endocrine disrupting properties of ipconazole for birds and fish. The applicant shall submit to the Commission, the Member States and the Authority the information under (a) and (b) by 31 August 2016, the information under (c) within two years after adoption of the pertinent guidance document on evaluation of isomer mixtures
Confirmatory information for ED requested/submitted	Technical report available for the points on granivorous birds and soil organisms. No data on ED. Overall, it was considered that the confirmatory data did not resolve the long-term risk to granivorous birds; SANTE has suggested to leave it to MS for mitigation. As regards soil macro-organisms, new studies were available and the updated risk assessment indicated a low risk. Deadline for application for renewal of approval 2021
EFSA/ECHA Guideline	Only data on birds and fish requested, but even these not submitted
PAN Europe observations regarding patterns in decision taking	The word "endocrine" is missing in the chapter on mammalian toxicity (only regarding fish, birds, etc.). Remarkable since ED-effects have been demonstrated, steroid synthesis (Benaki). Still in 2014 ED-effects on humans disregarded. Double strange since for other triazoles (like Bromuconazole in 2011) ED-test are mandatory.

Pesticide & classification	18. 2,4-D One of the 32 of JRC/Benaki.
Is ED evidence reported by industry (EFSA)?	Adverse effects on endocrine organs have been observed in apical studies that may be endocrine-mediated, which should be further clarified to assess their relevance on the developing offspring.
Is ED evidence reported by industry (IA)?	**YES, ED-adverse carc:** *Decreased litter viability and pup survival during lactation in rats, *Decreased lactation index and pup weight in rats, *Changes in adrenals weight and adrenal histopathology in rats are observed only in a 90-day study and not in longer duration studies, so they are disregarded due to low weight of evidence. * Increased absolute adrenals weight in mice (104 weeks) is disregarded since it was observed in the absence of any other ED-related effects. *Reduced fertility in rats (30 and 45 days) One study only, short term exposure. Low weight of evidence **YES, ED-adverse repro:** *Increased relative thyroid weight in rats (90-day & 2-year), *Delayed preputial separation and decreased LABC and prostate weight in rats, *Decreased testis weight, accessory sex glands weight, decreased histopathological changes in testes (small and soft testes, atrophy and degeneration of the seminiferous tubules) and decreased sperm count in rat, *Paraovarian cysts in rats (90 days), - low weight of evidence, *Histopathological findings in the thyroid in rat (24-month) are disregarded since it is not clear if it was considered significant or treatment related and treatment-related effects were not observed in the thyroid follicles [RAR]. Consequently, histopathological findings in the thyroid observed in the 90-day study are considered of low weight of evidence. **YES, effects on ED-organs:** *Decreased testosterone levels in rats, *Decreased serum T4 and/or T3 levels in mice and rats, *Weak competition for thyroxine binding sites in serum, *Decreased LH and FSH in rats
Is ED evidence reported in public literature?	
Commission's approval decision	January 2016 approval: In its conclusion EFSA points out there is evidence of potentially adverse endocrine effects on the thyroid hormone system which also might affect other organ systems. Furthermore, cases of increased adrenal weight and cortical hypertrophy have been reported. Considering however that these effect only occurred at levels far above the levels derived from the most critical mammalian toxicity studies that have been retained for setting the NOAEL, it may be assumed that any risk specifically linked to endocrine mediated effects is adequately covered by the current risk assessment.
ED Testing requirements	The notifier shall submit to the Commission, the Member States and the Authority: ….. (2) confirmatory information in the form of the submission of the Amphibian Metamorphosis Assay (AMA) (OECD (2009) Test No 231) as to verify the potential endocrine properties of the substance. The information …… set out in point (2) is to be submitted by 4 December 2017.
Confirmatory information for ED requested/submitted	Data submitted. Evaluation ongoing by RMS EL.
EFSA/ECHA Guideline	Just one test requested (TG 231)
PAN Europe observations regarding patterns in decision taking	High dose ED-effects dismissed. **Several ED-effects dismissed because of "low'weight of the evidence (PP?). Part of the JRC 32!!**

Pesticide & classification	**19. BENZOVINDIFLUPYR, CfS: 2 PBT (7 years)**
Is ED evidence reported by industry (EFSA)?	Considering the effects observed in the reproductive system of the two-generation reproductive toxicity study (reduced percentage of normal sperm in males of the P generation, reduced number of growing follicles and corpora lutea, and increased incidence of lactational diestrus in females of both P and F1 generations, delay of sexual maturation in offspring, while an increased incidence of hypertrophy of the adrenal zona glomerulosa was observed in adult females and increased incidence of cell hypertrophy in the pars distalis of the pituitary were observed in adult males at the top dose), it cannot be excluded that benzovindiflupyr is an endocrine disruptor.
Is ED evidence reported by industry (IA)?	No information
Is ED evidence reported in public literature?	
Commission's approval decision	February 2016
ED Testing requirements	Nothing on ED effects! However, on the basis of the effects observed in the reproductive system of the two-generation reproductive toxicity study (reduced percentage of normal sperm in males of the P generation, reduced number of growing follicles and corpora lutea, and increased incidence of lactational diestrus in females of both P and F1 generations, delay of sexual maturation in offspring, while an increased incidence of hypertrophy of the adrenal zona glomerulosa was observed in adult females and increased incidence of cell hypertrophy in the pars distalis of the pituitary were observed in adult males at the top dose), it cannot be excluded that benzovindiflupyr is an endocrine disruptor.
Confirmatory information for ED requested/submitted	Potential ED, but OECD level 2 only required in future after criteria are set (different from Flupyradifurone with CD)
EFSA/ECHA Guideline	OECD level 2 in future!
PAN Europe observations regarding patterns in decision taking	Policy seems to be no ED-testing for human RA untill criteria are set (another 10 years without testing?) .

Pesticide & classification	20. BROMUCONAZOLE, CfS: 2 PBT, Resubmission
Is ED evidence reported by industry (EFSA)?	Bromuconazole belongs to the group of triazole fungicides that are suspected to have potential endocrine disrupting properties. No information was provided to address this point with regard to the potential effects on birds and fish, and a data gap was identified. No new information on this point was provided in the Additional Report and the data gap remains.
Is ED evidence reported by industry (IA)?	**YES, ED-adverse carc:** *Changes in fetal development: irregular/incomplete ossification or neck bone variants; ↑7th cervical ribs (supernumerary bones), increased incidences of incomplete ossification (rabbit); (rat)], *Increased placental weight (rat)], Increased adrenal weight and decreased pituitary weight in rat are observed only in a 90-day study and not in longer duration studies, so they are disregarded due to low weight of evidence. **YES, ED-adverse repro:** *Changes in estrus cyclycity (acyclycity) (rat) **NO (secundary):** *Increased thyroid weight in rat is probably attributed to liver enzyme induction, which is not considered to be an ED-mediated mechanism. Therefore, these effects have not been considered for the evaluation as not informative to conclude on ED.., *Increased adrenal weight and changes in adrenals histopathology in dog are observed in presence of general systemic toxicity, *Abortions, resorptions and decreased number of live fetuses in rabbit occur in presence of maternal toxicity, *Increased gestation length, decreased litter/pup weight, decreased litter viability and changes in pup development (systemic toxicity) are observed in presence of parental toxicity, *Decreased fetal weight in rat is observed in presence of maternal toxicity (including mortality in one study).
Is ED evidence reported in public literature?	
Commission's approval decision	February 2011
ED Testing requirements	The Member States concerned shall ensure that the applicant submits to the Commission further information addressing the potential endocrine disrupting properties of bromuconazole within two years after the adoption of the OECD test guidelines on endocrine disruption or, alternatively, of Community agreed test guidelines.
Confirmatory information for ED requested/submitted	Confirmatory data requirement was set 'within 2 years' after the adoption of OECD or Community guidelines' No data submitted thus far.
EFSA/ECHA Guideline	Againfutile rule on two-years after OECD (this is August 2014)
PAN Europe observations regarding patterns in decision taking	2011-policy seems to be only ED-testing 2 years after adoption of EU (or OECD) test guidelines (this is the standard line used in decisions at that time) 3 years of prolongation while being a CfS (?).

Pesticide & classification	21. FLUPYRADIFURONE
Is ED evidence reported by industry (EFSA)?	With regards to the assessment for a potential endocrine-mediated mode of action, in a two-generation reproductive toxicity study, reproductive effects characterised by reduced number of oestrous cycles, reduced litter size and reduced number of implantation sites were observed at doses indicative of parental and offspring's toxicity such as decreased body weight and body weight gain. Although the reduced body weight may be an explanation for the reproductive effects observed, the experts agreed that there was insufficient evidence demonstrating that the mode of action was not endocrine-mediated and a data gap was set for Level 2 tests currently indicated in the OECD Conceptual Framework (OECD, 2012), and analysed in the EFSA Scientific Opinion on the hazard assessment of endocrine disruptors (EFSA, 2013), noting that further tests might be necessary pending on the outcome (issue not finalised).
Is ED evidence reported by industry (IA)?	No information
Is ED evidence reported in public literature?	
Commission's approval decision	2015
ED Testing requirements	However, an endocrine-mediated mode of action could not be ruled out regarding the reproductive effects observed in the multigeneration toxicity study (reduced number of implantation sites and oestrus cycle, reduced litter size - reduced number of pups born and higher number of stillborn) and the potential for endocrine disrupting effects could not be finalised
Confirmatory information for ED requested/submitted	na.
EFSA/ECHA Guideline	
PAN Europe observations regarding patterns in decision taking	EFSA indicates need for OECD level 2 tests, nothing in decision (?). (Though already suggesting reason to dismiss effects).

Pesticide & classification	22. GLYPHOSATE
Is ED evidence reported by industry (EFSA)?	Previously EFSA noted that for certain effects observed in one study at parental toxic doses, signs of endocrine activity could not be completely ruled out and a data gap was identified. The current assessment concluded that the weight of evidence indicates that glyphosate does not have endocrine disrupting properties through oestrogen, androgen, thyroid or steroidogenesis mode of action based on a comprehensive database available in the toxicology area. The available ecotox studies did not contradict this conclusion. Glyphosate shows no endocrine-mediated adverse effects in apical studies; the weak evidence in a limited number of supplementary in vitro studies was inconsistent with the findings of the acceptable OECD tests and it was not expressed in vivo in the OECD level 4 and 5 studies, and no EATS-mediated endocrine mode of action was identified.
Is ED evidence reported by industry (IA)?	**YES, ED-adverse repro:** *Delay in preputial separation and decrease in homogenisation resistant spermatids in rat (Study ID 15). [Apical studies did not show adverse effects on the reproduction, however signs of endocrine activity, even if appearing at parental toxic doses, could not be completely ruled out regarding delay in preputial separation in males and decrease in homogenisation resistant spermatids (cauda pididymis) observed in the most recent multigeneration study, EFSA Conclusion 2015]. Decreased prostate and uterus weight in dog at maximal dose; Not reproducible effects; Disregarded **NO (secundary):** Decreased pup weight in rat at parental toxic dose (decreased body weight, clinical signs), Decreased ossification and slightly increased skeletal anomalies in rat at parental toxic dose (decreased body weight gain, clinical signs), Abortions in rabbit in the presence of general adversity (mortality, clinical signs), Increased post implantation loss in rabbit in the presence of general adversity (decreased body weight gain), Decreased ossification in rabbit at maternal toxic dose (decreased body weight gain, food consumption)
Is ED evidence reported in public literature?	Teratogenic effects reported in open literature
Commission's approval decision	Dec-17
ED Testing requirements	No
Confirmatory information for ED requested/submitted	
EFSA/ECHA Guideline	
PAN Europe observations regarding patterns in decision taking	

Pesticide & classification	23. L-CYHALOTHRIN, 2x CfS, 2PBT, low ADI etc.
Is ED evidence reported by industry (EFSA)?	With regard to the assessment for a potential endocrine mode of action, some in vitro studies from the open literature describe interactions of lambda-cyhalothrin with receptors of the endocrine and immune systems. Considering the sperm effects in mice (see above) and the brain morphological changes in the developmental neurotoxicity study, the available data are not sufficient to clarify the potential endocrine activity. data gap level 2/3 OECD tests
Is ED evidence reported by industry (IA)?	**YES, ED-adverse carc:** Mammary gland adenocarcinomas in mice, Decrease in pup/litter weight and survival after birth in rats. **YES, toxic ED-organs:** Decreased T3, T4 in rat & controversial results in TSH levels in rat . **YES, ED mechanistic:** Weak antiandrogenic activity, oestrogenic activity, thyroid receptor antagonistic effects. **YES, ED-link**: - Plausible link of mammary gland adenocarcinomas in mice with oestrogenic activity, [RAR: lambda-cyhalothrin acts likely via a mechanism similar to that of 17β-estradiol], - No link of in vivo mechanistic to adverse effects - data gap raised by EFSA for testicular and sperm examination
Is ED evidence reported in public literature?	Based on in-vitro studies in inde lit L-cyhalothrin may affect endocrine function; the results of these studies cannot be disregarded in absence of testing according to guidelines (RAR 2013, RMS SE). Four in vivo mammalian independent studies published show effects on thyroid hormones, sperm , testis and immunity; not taken into account in regulatory dossier (other formulation; lack of detailed description). In total at least 12 independent studies are available.
Commission's approval decision	April 2016: No mentioning of ED-effects. Rational: no specific indication is available that the morphometric changes in the cerebellum of foetuses are determined via one of the EATS (oestrogen, androgen, steroidogenesis and thyroid) axis. Therefore no specific OECD validated test methods could be described.
ED Testing requirements	No ED-tests. A systematic review to assess the evidence available as regards potential sperm effects linked to exposure to lambda-cyhalothrin using guidance available (e.g. EFSA GD on Systematic Review methodology, 2010);
Confirmatory information for ED requested/submitted	No CI
EFSA/ECHA Guideline	
PAN Europe observations regarding patterns in decision taking	EFSA concludes to data gap for OECD level 2/3; SANTE disregards the conclusion and denies any ED-effect. Benaki shows ED/carc, mechanistic and a link; curious that SANTE ignores all this evidence (PP?). While 4 independent in-vivo studies report effects on thyroid hormones, sperm , testis and immunity, no further ED-testing is done In case of doubt, SANTE always choses for non-ED; violation precautionary principle Full ED acc. to JRC/Benaki (not part of 32 - ?)

Pesticide & classification	**24. PROPYZAMIDE, C2, CfS: 2PBT** **One of the 32 of JRC/Benaki.**
Is ED evidence reported by industry (EFSA)?	Further investigations of potential endocrine-mediated effects were performed in a battery of in vitro and in vivo assays. Based on the available results, propyzamide was concluded as unlikely to have a direct effect on receptors of the endocrine system, including oestrogen, androgen and thyroid pathways. The antiandrogenic and antioestrogenic effects of propyzamide are likely to occur through modulating the metabolism of steroid hormones by inducing the liver metabolising enzymes. During the peer review, some concerns were raised regarding some alterations of the male vitellogenin (VGT) level and histopathological findings observed in one of the two short-term reproduction assays carried out with fish.
Is ED evidence reported by industry (IA)?	**YES, ED-adverse carc:** Mammalian data: Adrenal histopathology findings (rat) (rat), rat), Increased adrenal weight, (dog),(mouse), (rat), Decreased pup weight, (rat), Altered pituitary histopathology, (rat),(rat), (rat), (rat), (rat), Adverse effects on adrenals have been reported in many studies . Since these effects have been observed in different species (dog, mouse, rats) they should not be excluded from the evaluation / categorization procedure, although in some cases they have not been observed in studies with longer duration. **YES, ED-adverse repro:** Mammalian data: Ovary histopathology findings,(rat), Testis histopathology alterations,(rat), rat), (rat), Testis discoloration, size variation and enlargement, (rat), Increased testis weight, (rat), Increase Age at preputial separation, Decrease in Coagulating gland weight, LABC weight, prostate weight and Seminal vesicles weight, Altered thyroid histopathology, (rat), (rat), (rat), (rat), (rat), (rat),increased thyroid weight, (rat), (rat), (rat). **YES, ED-link:** The available in vivo mechanistic data (i.e. decreased T4 and increased TSH levels) are in concordance with the observed thyroid effects (increased thyroid weight, thyroid hypertrophy and hyperplasia)
Is ED evidence reported in public literature?	Effects potentially caused by disruption of endocrine systems were observed (thyroid and testicular tumours and ovarian hyperplasia); Evidence of endocrine disruption leading to formation of thyroid tumours (DAR 1998/CRD); Hormonal changes affecting the pituitary-testicular endocrine axis; thyroid follicle cell adenoma, benign Leydig cell tumours in rats and liver tumors in mice (SANCO rr)
Commission's approval decision	2018, nothing on ED-effects (now fully adopted EFSA's conclusion)
ED Testing requirements	No testing requirements
Confirmatory information for ED requested/submitted	na.
EFSA/ECHA Guideline	
PAN Europe observations regarding patterns in decision taking	Earlier SANTE review reports mentioned hormonal changes on pituitary-testicular axis. **Benaki demonstrates ED-adverse effects and a plausible link.** **In case of doubt, SANTE always choses for non-ED; violation precautionary principle** **One of the 32 of JRC/Benaki.**

Pesticide & classification	25. THIABENDAZOLE
Is ED evidence reported by industry (EFSA)?	Thyroid adenomas and follicular cell hyperplasia occurred in rats due to liver enzyme induction. Relevant scientific peer-reviewed open literature on the potential endocrine activity of thiabendazole, reported as being available, has not been provided in the dossier and a data gap has been identified. No investigations have been provided to clarify a possible endocrine-mediated mode of action of thiabendazole. Therefore, a data gap is identified for investigation of potential endocrine-mediated effects of thiabendazole
Is ED evidence reported by industry (IA)?	**YES, ED-adverse carc:** Resorptions (rabbit) **YES, ED-adverse repro:** Decreased ovary weight (mouse), Ovary histopathology: atrophy, cyst (mouse), Decreased testis weight (mouse), Decreased uterus weight (mouse), Uterus histopathology: cystic endometrial hyperplasia (mouse), Penis histopathology: grandular atrophy of the preputial gland (mouse), Seminal vesicles histopathology: cystic dilatation (mouse), (All the adverse effects observed are from one chronic study in mouse but they are considered adequate weight of evidence) **YES, ED mechanistic:** Estrogen receptor (ERα and ERβ transactivation in human HeLa cells)] and (estrogenic activity in BG-1 ovarian cells)], Increase in proliferation of MtT/Se rat pituitary tumor cell line expressing ERα and ERβ, Induction of estrogenicity through displacement of TCDD from AhR.
Is ED evidence reported in public literature?	
Commission's approval decision	Apr-17
ED Testing requirements	The applicant shall submit by 31 March 2019 to the Commission, the Member States and the Authority confirmatory information regarding Level 2 tests as currently indicated in the OECD Conceptual Framework investigating the potential for endocrine-mediated effects of thiabendazole.
Confirmatory information for ED requested/submitted	Not yet
EFSA/ECHA Guideline	
PAN Europe observations regarding patterns in decision taking	Do the new criteria and guidance apply? This time EFSA requires OECD level 2, also in case no clear ED-information is available. Why is this not done for every pesticide? Full ED acc. to JRC/Benaki (not part of 32).

Pesticide & classification	26. TRIFLOXYSTROBINE, R2 and toxic for ED organs (IC)
Is ED evidence reported by industry (EFSA)?	Effects on endocrine organs (pancreatic atrophy in the 90-day rat study, adrenal tumours in the 2-year rat study) at cytotoxic dose levels or doses exceeding the maximum tolerable dosage and the lack of in vitro oestrogen, androgen, thyroid receptors and aromatase-mediated activity, the experts agreed that trifloxystrobin should be considered as unlikely to be endocrine disruptor in mammals
Is ED evidence reported by industry (IA)?	**YES, mechanistic:** Estrogen receptor; Very potent ERα antagonist, ERα-dependent proliferation (medium potency), The substance was inactive in all the other tests included in the ToxCast database excel file.
Is ED evidence reported in public literature?	
Commission's approval decision	2018
ED Testing requirements	no ED-testing required
Confirmatory information for ED requested/submitted	na.
EFSA/ECHA Guideline	
PAN Europe observations regarding patterns in decision taking	The pesticide has clear (very potent) ED-properties; still no additional ED-testing required. If vitro positive and vivonegative: NO ENDOCRINE If vitro negative and vivopositive ((Trifloxystrobin): NO ENDOCRINE

Pesticide & classification	27. CHLORPYRIFOS
Is ED evidence reported by industry (EFSA)?	the experts agreed not to highlight the general concerns and the specific concerns on genotoxicity, endocrine disruption and developmental neurotoxicity in the EFSA conclusion (2014).
Is ED evidence reported by industry (IA)?	Benaki, Repro-related ED-effects (YES): Effect on sperm number, Changes in testis histopathology: serious damage to the laminar basement membrane, shrinkage of the tubular diameter, degenerative changes in the germinal epithelium and incomplete spermatogenesis, Decrease testis weight, Increase ovary histopathology, Increase uterus histopathology, Decrease estrus cyclicity, Decrease ovary weight, Decrease sperm motility, Decrease Steroidogenesis (genes/enzyme changes), Increase thyroid histopathology, Decrease uterus weight, Increase vaginal smears. Toxic effects endocrine organs: Decrease FSH level, Decrease LH level, Decrease testosterone level, Decrease estradiol level, Decrease Glans penis weight (Hershberger), Decrease T3/T4 level. Benaki, ED-organs-related ED-effects (YES): Decrease FSH level, Decrease LH level, Decrease testosterone level, Decrease estradiol level, Decrease Glans penis weight (Hershberger), Decrease T3/T4 level. Chlorpyrifos generally negative in EDSP testing
Is ED evidence reported in public literature?	
Commission's approval decision	Revision in 2014 because of developmental neurotoxicity (Rauh studies).
ED Testing requirements	No tests for ED
Confirmatory information for ED requested/submitted	na.
EFSA/ECHA Guideline	
PAN Europe observations regarding patterns in decision taking	is it possible to revise a pesticide without looking at ED (current scientific insights)?

Pesticide & classification	28. IPROVALICARB
Is ED evidence reported by industry (EFSA)?	On the basis of the pattern of tumours observed in the long-term toxicity study in rats, it cannot be excluded that iprovalicarb is an endocrine-disruptor.
Is ED evidence reported by industry (IA)?	**YES, ED-adverse carc**: Increased incidence of mixed Muellerian tumours in the uterus (rat), decreased lactation index (rat). **No (secundary):** The thyroid follicular cell adenoma/carcinomas may be attributed to liver enzyme induction (increased liver weight and hypertrophy at the same dose level). This mechanism is not considered to be an ED-mediated mechanism. Therefore, these effects have not been considered for the evaluation as not informative to conclude on ED. The decreased pup weight was observed at maternal toxic dose.
Is ED evidence reported in public literature?	
Commission's approval decision	2016
ED Testing requirements	
Confirmatory information for ED requested/submitted	Confirmatory information in the form of the submission of the Level 2 tests (OECD, 2012) as to verify the potential endocrine properties of the substance
EFSA/ECHA Guideline	Level 2
PAN Europe observations regarding patterns in decision taking	This time OECD testing; what is the policy??

Pesticide & classification	29. TOLCLOFOS-METHYL
Is ED evidence reported by industry (EFSA)?	the experts agreed that there was no evidence of endocrine-mediated effects in vivo; therefore, the experts concluded that tolclofos-methyl is unlikely to have endocrine disrupting properties.
Is ED evidence reported by industry (IA)?	**YES, ED adverse effect,** Increased pituitary weight **YES, mechaanistic information:** Estrogen receptor_agonistic activity; Estrogen receptor (increased Erα and Erβ agonistic activity); Androgen receptor_ antagonistic activity; ER alpha-dependent cellular proliferation
Is ED evidence reported in public literature?	
Commission's approval decision	June 2019 (ornamentals and potatoes)
ED Testing requirements	No test for ED
Confirmatory information for ED requested/submitted	na.
EFSA/ECHA Guideline	EFSA tends to easily dismiss potential ED activity
PAN Europe observations regarding patterns in decision taking	

Pesticide & classification	30. FLORPYRAUXIFEN-BENZYL
Is ED evidence reported by industry (EFSA)?	No evidence of endocrine or reproductive toxicity were seen in the whole toxicology data package except for reduced ovary weights in the 90-day mice study and mammary gland tumours in males in the 2-year rat study. A data gap was set to clarify a potential endocrine-mediated mode of action with a minimum of in vitro studies (e.g. oestrogen receptor binding and transduction assay). It is noted that the RMS did not agree with this data gap since it considered the mammary gland tumours as non-treatment-related
Is ED evidence reported by industry (IA)?	not assessed
Is ED evidence reported in public literature?	
Commission's approval decision	24 July 2019
ED Testing requirements	The Commission considers that florpyrauxifen-benzyl does not have endocrine disrupting properties based on the available scientific information summarised in the conclusion of the Authority. However, in order to increase the confidence in this conclusion, the applicant should provide an updated assessment
Confirmatory information for ED requested/submitted	The applicant shall submit to the Commission, the Member States and the Authority an updated assessment of the information submitted and, where relevant, further information to confirm the absence of endocrine activity in accordance with points 3.6.5 and 3.8.2 of Annex II to Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) 2018/605 by 24 July 2021
EFSA/ECHA Guideline	No requirement for level 2/3 EFSA advised in vitro studies not obliged
PAN Europe observations regarding patterns in decision taking	What is updated assessment"? It is entrely up to industry to do testing or not.

Pesticide & classification	31. DIMETHENAMID-P
Is ED evidence reported by industry (EFSA)?	From a scientific perspective, it was noted that sensitive endpoints pertaining to the OECD level 5 (OECD, 2012) had not been investigated in the submitted multigeneration study or other studies such as thyroid hormone measurements; however, no concern arouse from the existing studies and mechanistic information available from the ToxCAST database did not indicate a biologically relevant interference of dimethenamid (racemic mixture) with the androgen, oestrogen or thyroid receptor pathways supporting the conclusion that dimethenamid-P is unlikely to present an endocrine-mediated mode of action.
Is ED evidence reported by industry (IA)?	not assessed
Is ED evidence reported in public literature?	
Commission's approval decision	3 July 2019
ED Testing requirements	the conclusion of the Authority indicates that, based on the scientific evidence, it is highly unlikely that dimethenamid-P is an endocrine disrupter and that no additional studies are considered necessary to be carried out. Thus, the Commission concludes that dimethenamid-P is not to be considered as having endocrine disrupting properties.
Confirmatory information for ED requested/submitted	no
EFSA/ECHA Guideline	
PAN Europe observations regarding patterns in decision taking	Endocrine sensitive endpoints not tested! Conclusion "highly unlikely". In case of lacking data: SAFE.

Pesticide & classification	32. MEFENTRIFLUCONAZOLE
Is ED evidence reported by industry (EFSA)?	From a scientific perspective, a weak inhibition of aromatase activity seen in vitro did not translate to any relevant adverse effect in vivo and it was concluded that mefentrifluconazole is unlikely to have ED properties regarding oestrogen, androgen, thyroid and steroidogenesis (EATS) modalities. The available test according to OECD TG 234 does not cover the reproductive life stages of fish. Considering the results of in vitro data (positive for aromatase inhibition) further information, e.g. a test according to OECD 229, should be provided in order to draw a firm conclusion the endocrine potential of mefentrifluconazole in fish.
Is ED evidence reported by industry (IA)?	not assessed
Is ED evidence reported in public literature?	
Commission's approval decision	27 February 2019
ED Testing requirements	the conclusion of the Authority infers that it is unlikely that mefentrifluconazole is an endocrine disrupter via the estrogenic, androgenic, thyroidogenic and steroidogenic modalities. Also nof for fish.
Confirmatory information for ED requested/submitted	no
EFSA/ECHA Guideline	EFSA concludes further testing is needed (OECD 229), but COM ignores the advice.
PAN Europe observations regarding patterns in decision taking	Even with the flawed fish endoc rine test, COM concludes to safety.

Pesticide & classification	33. METHOXYFENOZIDE
Is ED evidence reported by industry (EFSA)?	In the area of mammalian toxicology and non-dietary exposure, issues that could not be finalised included the endocrine potential of methoxyfenozide (regarding the scientific risk assessment) and the lack of an in vitro comparative metabolism study. With regard to the scientific risk assessment the majority of the experts agreed that more data (level 2 and level 3 studies according to OECD conceptual framework (OECD, 2012)) are needed in the light of the observed effects on thyroid such as changes in thyroid weight sometimes correlating with follicular cell hypertrophy and C-cell adenomas (data gap and issue that could not be finalised). The RMS did not agree
Is ED evidence reported by industry (IA)?	
Is ED evidence reported in public literature?	
Commission's approval decision	31 January 2019
ED Testing requirements	The conclusion of the Authority infers that it is highly unlikely that methoxyfenozide is an endocrine disrupter via the estrogenic, androgenic and steroidogenic modalities. Furthermore, the available evidence (amphibian metamorphosis assay) indicates that methoxyfenozide is unlikely to be an endocrine disruptor via the thyroid modality. Thus, the Commission considers that methoxyfenozide is not to be considered as having endocrine disrupting properties. Although it can be reasonably expected that metoxyfenozide is highly unlikely to have endocrine disrupting properties based on the available scientific information summarised in the conclusion of the Authority, in order to increase the confidence in this conclusion, in accordance with Point 2(2)(b) of Annex II to Regulation (EC) No 1107/2009, the applicant should provide an updated assessment of the information submitted and, where relevant, further information to confirm the absence of thyroid endocrine activity.
Confirmatory information for ED requested/submitted	The applicant shall also provide an updated assessment of the information submitted and, where relevant, further information to confirm the absence of thyroid endocrine activity in accordance with Points 3.6.5 and 3.8.2 of Annex II of Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) 2018/605(2), by 1 February 2021.
EFSA/ECHA Guideline	EFSA concludes OECD level 2/3 are necessary. COM only "updated assessment".
PAN Europe observations regarding patterns in decision taking	Again COM ignores EFSA advice on the need of level 2/3 tests.

Results

1. Most sensitive test never requested.

In none of the cases the most ED sensitive test available for adverse effects was requested, the extended one generation reproductive toxicity test[21] with the complete list of endocrine-related endpoints.

2. Delay ED evaluation for another 10 years.

In several of the studied cases (12 out of 33) "information" on ED-effects of the pesticide substance was requested (or information "within 2 years after adoption of OECD guidelines"), but in most cases where "information" was requested (10 out of 12) industry failed to deliver complete information to assess whether the substance is an ED for decision taking. Commission and Rapporteur Member States allowed this to happen and decided to start the proces again in renewal, which is 10 years later. Some examples of these ineffective moves are:

- Flurochloridone, 2011 decision, and renewal 2021
- Difenoconazole, 2009 decision and renewal 2019
- Epoxiconazole (R1B!), 2009 decision and 2020 renewal
- Ipconazole (fish, birds), 2014 decision and 2024 renewal
- Tetraconazole, 2010 decision, and renewal 2020

The end result in these 12 cases was always 10 years of delay, waiting for the next renewal turn. And since there are no data submitted (or "information" provided which is scientifically useless to assess EDPs), and the Rapporteurs do not take action to request the missing data, no regulatory action is foreseen by Commission on endocrine disruption. This allowed industry to submit information that by definition (given their conflict of interest) would not be usefull for regulatory action. In 3 out of the 12 cases (the pesticides Epoxiconazole, Prochloraz, Bromuconazole) Commission requested "studies" (called "confirmatory information") two years after the adoption of the OECD-guidelines (2014). However, this procedure followed by DG SANTE was just as useless as the others. Industry didn't deliver studies, and the Commission and the Rapporteur Member State apparently permitted it.

3. Request for updated assessment.

More recently, in 2019 (after adoption of the criteria), DG SANTE started to request an "updated assessment" (the pesticides Flutianil, Isoxaflutole, Florpyrauxifen, Methoxyfenozide) from the industry applicant. It remains to be seen if this "updated assessment" will have any value over "information" since there will be little doubt that industry will use this updated assessment as well to claim that their pesticide is not an EDP. And very likely it will not generate additional ED-specific data to submit. This approach of not generating data serves to reduce costs for industry but doesn't help identifying EDPs and protecting the public, animals and wildlife.

21. www.oecd-ilibrary.org/environment/test-no-443-extended-one-generation-reproductive-toxicity-study_9789264185371-en

4. Minor requests for ED-specific testing.

DG SANTE, only in very few cases (4 out of 33), does request ED-testing (OECD equivalent level 2 or 3 tests) when specific information on one of the EATS (Estrogen, Androgen, Thyroid, Steroidogenesis) axis is available in the traditional application dossier indicating that the substance may be an endocrine disruptor. This was the case in 2016 for Iprovalicarb (OECD level 2), in 2017 for Mesotrione OECD level 2/3 (Syngenta submitted two level 2 studies so far) and Thiabendazol (level 2 still in due), and Bentazon in 2018 (OECD level 2/3) after EFSA identified a data gap. Interestingly, in 4 other cases where EFSA had identified data gaps on 2/3 level OECD testing (the pesticides L-cyhalothrin, Flupyradifurone, Mefentrifluconazole, Methoxyfenozide) its scientific advice seems to have been ignored, since DG SANTE did not request any additional studies.

5. A consistent policy on ED-testing is lacking.

Overall, a consistent policy on testing of EDPs is lacking. DG SANTE has refused to request specific ED-testing (OECD level 2/3) for every pesticide active sustance currently in the market to identify ED-properties. This is a way to say that ED-properties should not be tested by carrying out specific and ED-sensitive studies. As if ED is just one of the properties that any chemical can have and that adverse effects will be anyway observed in standard chronic testing and that ED activity doesn't require extra attention or specific testing. This approach contradicts the scientific principles of endocrinology and is a clear obstruction of EU endocrine disruption policy that aims to protect the public against this kind of special endocrine-related toxicity that was not considered in the past, despite the numerous evidence. The fact that the OECD developed a set of sensitive tests to identify some EDPs makes it clear that past animal testing was not designed to identify EDPs.

6. Breaking the rules by applying potency.

If ED-effects are observed, they're still dismissed if they are above the lowest No Observed Adverse Effect Level , NOAEL, (2,4-D, Trifloxystrobin, Flutianil, Epoxiconazole) for another observed adverse effect. The level of the endocrine disrupting chemical at which it caused harm cannot not be the decisive factor to decide if a chemical is an endocrine disruptor. Therefore one can conclude that DG SANTE applies the potency principle. This is against the political decisions not to apply potency.

7. Decisions contradict results in Commission's own preliminary study.

ED-pesticides that have already been identified by JRC/Benaki2[2] (the pesticides Flurochloridone, L-Cyhalothrin, Prochloraz, 2,4-D, Propyzamide, Epoxiconazole, Pendimethalin) do not get a special attention. The identification did not trigger a review of the subtance's approval (Art.21 procedure) or the requirement to do additional (OECD) testing. Pendimethalin is even considered to have no ED-activity (2017) at all. This shows the weak side of the so-called "expert judgement" (the opinions and feelings of those experts being present in a meeting or panel): EFSA experts say Pendimethalin is not an EDP, while Benaki experts say it is an EDP (Benaki: ED adverse effects on reproduction via the thyroid, toxic to thyroid as anendocrine organ, mechanistic data provide for a link between activity and adverse effect). The same happened with the pesticides Propyzamide and L-cyhalothrin. The EDPs Epoxiconazole, Prochloraz, 2,4-D and Tetraconazole are still in their 10-years approval period and not re-assesed.

22. https://ec.europa.eu/health/sites/health/.../endocrine.../2016_impact_assessment_en.pdf

8. Dismissing repeatedly adverse effects using unscientific and non transparent reasons.

Endocrine adverse effects are dismissed using Historical Control Data (HCD), an unscientific risk assessment approach (increasing control values[23] to hide toxicity). This type of assessment is not used by academic scientists; concurrent controls are normally used to compare the exposed groups. The use of HCD to reject adverse effects seen in exposed groups because they are within the range of historical control data, was invented by industry to get chemicals qualified "safe" by increasing the control values. It is completely unscientific and a clear manipulation of the outcome of animal testing to get a desired outcome. Similar non-scientific assumptions are used like "indirect effect" (Fluopyram), "only at high dose" (2,4-D, Flurochloridon, Trifloxystrobine), 'likely other mechanisms" (Propyzamide), "non-treatment related" (Florpyrauxifen), all assunmptions without providing underlying experimental data for the chemical in question.

9. ED interim criteria were never implemented.

At the time that the interim criteria were in force (criteria that counted untill the final ED-criteria were set by Commission in 2018), for example for pesticides with a classification R2+C2 like Acibenzolar-methyl, Flutianil, Isoxaflutole, Mesotrione, DG SANTE did not manage to get a single non-approval based on these criteria. This bypassing of the legal obligation was very much supported by the Standing Committee which consists of representatives of national agricultural ministries, representatives with a main interest of keeping pesticide products available for their farmers.

10. Copying results from US testing.

The outcome of US-EDSP testing[24] is taken for granted while the US-policy is not in agreement with the EU system system. The US applies "potency", effects seen at higher level are disregarded and the US dismisses many observed effects observed as non-endocrine related without much experimental evidence.

11. Dismissing endocrine related adverse effects from peer-reviewed scientific literature.

Independent studies do not play a significant role in the assessment of pesticides and in many cases they are not even collected by EFSA unless they've been submitted in the public consultation. EFSA drafted their opinion while disregarding all adverse effects observed in studies from open scientific literature (e.g. in the case of the pesticides Difenoconazole, Prochloraz, L-Cyhalothrin). For Prochloraz there are at least a dozen studies in the public domain that show ED-activity and adverse effects (In vitro MoA: Strong: aromatase inhibition, anti-estrogenic and anti-androgenic; In vivo MoA: Strong: anti-androgenic; Adverse effects: Strong; Anti-androgenic, nipple retention; Plausible link: Strong). From a scientific point of view it is misconduct to ignore these data and from a legal point of view unlawful since the scope of Regulation 1107/2009 is to ensure that pesticides "do not adversily affect human or animal health or the environment" (Article 1.4;).

12. Commission decision taking without ED-testing.

In case EFSA concludes that endocrine activity "cannot be excluded" (the pesticide Thifensulfuron), and adverse effects have been observed in vitro (estrogen and

23. Writing IOR
24. www.epa.gov/endocrine-disruption/endocrine-disruptor-screening-program-edsp-overview
25. www.efsa.europa.eu/en/press/news/180607

androgen receptor activation) as well as in vivo (mammary gland tumours in rats), DG SANTE requests confirmatory information "to rule out" endocrine activity, but does not request the ED-specific tests. However, without ED specific testing ED cannot be ruled out (see Guideline on the identification of EDs[25], page 32).

13. Data gaps do not trigger testing requirements.

In case EFSA concludes there is a "data gap" on endocrine activity (the pesticide Flutianil, level 2 tests and endocrine-relevant adverse effects have been observed in vivo) , SANTE requests an updated assessment of the information and does not request ED-specific tests to "confirm" that the susbtance is not an EDP. In case of doubt SANTE assumes no endocrine activity, turning the implementation of the precautionary principle upside down.

14. New EU Guideline ignored.

The EFSA/ECHA Guidance on EDPs[26] is very clear on page 32 on testing requirements: "Based on the current knowledge and available test guidelines, to consider the EATS-related endocrine activity sufficiently investigated with respect to humans and mammals (as non-target organisms), the information described below **needs to be available** in order to support a conclusion on absence of EATS-related endocrine activity"[27]. For the so-called EATS modalities (different axis of the endocrine system), the Guideline clearly describes the minimum required testing.

15. Commission only covers part of ED-activity.

It has to be noted that Commission limits itself tot he so-called EATS-related endocrine acitivity and disregards any other types of endocrine activity that are capable of disturbing the function of the hormonal system irreversably[28] such as immune related disorders, neurodevelopmental and metabolic diseases.

26. www.efsa.europa.eu/en/press/news/180607

27. E-modality – The output data from the ToxCast ER Bioactivity Model or 'Uterotrophic bioassay in rodents' (OECD TG 440) (OECD, 2007d).

A-modality – 'Hershberger bioassay in rats' (OECD TG 441) (OECD, 2009d).

T-modality – In vitro mechanistic test guidelines for the T modality are currently not available as well as specific in vivo mechanistic tests on mammals. Hence, to consider the T modality as 'sufficiently investigated' for mammals the thyroid parameters foreseen to be investigated in the following studies OECD test guidelines 407, 408, 409 (and/or the one-year dog study, if available), 416 (or 443 if available) and 451-3 should have been measured and the results included in the dossier (see Section 3.4.1).

S-modality – The level 2 in vitro assays 'H295R steroidogenesis assay' OECD TG 456 (OECD, 2011c) and the 'aromatase assay (human recombinant)' OPPTS 890.1200 (US EPA, 2009b). There are currently no level 3 tests that fully cover this modality, however it is partially covered by OECD TG 441. Therefore, the results of the above in vitro assays should be considered together with the results of the E and A modalities in order to conclude on the absence of endocrine activity for the S modality. To consider the E, A, S modalities for non-target organisms other than mammals sufficiently investigated, preferably the 'Fish short term reproduction assay' (FSTRA; OECD TG 229) should have been conducted; however the 21-day fish assay OECD TG 230 (OECD, 2009b) is acceptable as well. If data are already available covering the mechanistic parameters investigated in OECD TG 229 or OECD TG 230 (e.g. OECD TG 234), then those data could be used instead.

To consider the T-modality sufficiently investigated, an 'Amphibian metamorphosis assay' (AMA; OECD TG 231 (OECD, 2009c)) should have been conducted.

28. https://publ ications.europa.eu/en/publication-detail/-/publication/6b464845-4833-11e8-be1d-01aa75ed71a1/language-en . Test that are lacking are:

Tests both for human health and the environment covering additional hormonal pathways and modalities besides the oestrogen, androgen, thyroid and steroidogenesis ('EATS');

Animal models in relation to certain human endocrine disorders in which endocrine disruptors have been suggested to play a role, such as some mammary gland tumours and other hormonal cancers, endometriosis, metabolic syndrome or reproductive senescence;

A single study involving observations through the complete life cycle of a mammal, from conception to old age, which would cover all specific windows of susceptibility in order to cover effects that might be induced by exposure during foetal or pubertal development that only emerge during later life stages e.g. cancer incidence in adult or aged animals; and

Appropriate tests for environmental species (beyond fish and mammals) such as birds and invertebrates.

Conclusion

EFSA, DG SANTE and several EU Member States have great difficulty accepting that endocrine disruption is a new health "hazard" class that needs to be adressed and properly regulated to protect human, animal and environmental health . They fiercely defend traditional risk assessment methods that have been applied in the past when endocrine disruption, regretably, was not a specific requirement of assessment. This new PAN Europe survey reveals that ED-specific testing is not provided (none for adverse effects and only in 4 cases for endocrine activity). Many potential endocrine disrupting effects observed are downplayed with views like "indirect effect", "only at high dose" (2,4-D), 'likely other mechanisms" (Propyzamide), "within historical control data" (Flutianil), all speculations based on little experimental evidence. In the best case it is concluded that "endocrine effect couldn't be excluded" and "information is needed to confirm absence of ED-activity". Again, it seems that regulators are not trying to identify harmful toxic endocrine disruptors, but do their best to dismiss observed adverse effects that could be related to endocrine disruption. Even when EU JRC/Benaki conclude that a substance is an ED (ED-properties, ED-adverse effects and ED-mechanistic link), the regulators question the observed effects and asks for more information (the pesticides Flurochloridone, L-Cyhalothrin, Prochloraz, 2,4-D, Propyzamide, Epoxiconazole, L-cyhalothrin, Pendimethalin), and even describe some of the observed adverse effects (Pendimethalin, Propyzamide) as non-endocrine related. The regulators also apply "potency" (Flutianil, 2,4-D, Trifloxystrobin), the element that was decided to be left out the ED-definition of the criteria. This is illegal and disloyal. It shows once again the continuous opposition in EU Commission to properly implement the rules on endocrine disruption.

It is evident that the regulators resist to identify endocrine-related effects. They generally do not study independent literature and are trying to play down the observed adverse effects to a marginal element and maintain that their assessments in the past have always been robust. Nevertheless, toxicology has moved on, we know more about the toxicity of chemicals and we now discover that many chemicals are not safe to be used as pesticides

The result of this failing policy is that ED-data are virtually absent. EU Commission did not put in place a general obligation to test pesticides for endocrine effects, even not when agreed and verified international guidelines (OECD level 2/3 as a first step of identification) are available. This means that specific, subtle, low dose, endocrine effects are not studied and the public and the environment is not sufficiently protected. The regulators stick to the old, outdated protocols from the last 40 years and claim that these protocols also protect against endocrine disruption. This is undermining political adopted rules (Regulation 1007/2009) on endocrine disruption and undermining a scientific consensus[29]. Only in very few cases when EFSA decides to a "data gap" on

29. www.ncbi.nlm.nih.gov/pmc/articles/PMC4702494/

endocrine disruption and OECD tests, DG SANTE requests from industry to carry out level 2/3 test, but in most cases it doesn't. In the majority of the cases only "information" or an "updated assessment" is asked from industry, without the need (and costs) of testing, leaving it up to industry what to deliver. Industry will never deliver information that would lead to the identification of an EDP.

This leaves us with this vicious circle:

30. EFSA opinion endocrines, EFSA Journal 2013;11(3):3132: "EDs can therefore be treated like most other substances of concern for human health and the environment"

31. "Quod Erat Demonstrandum" which loosely translated means "that which was to be demonstrated".

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