

TECHNICAL REPORT

ANALYSIS OF EUROPEAN GLYPHOSATE RISK ASSESSMENT AND THE IRRATIONAL DISMISSAL OF STUDIES THAT REPORT TOXIC EFFECTS

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ANALYSIS OF EUROPEAN GLYPHOSATE RISK ASSESSMENT AND THE IRRATIONAL DISMISSAL OF STUDIES THAT REPORT TOXIC EFFECTS

[RAPPOORTEUR MEMBER STATE: GERMANY (WITH SLOVAKIA AS CO-RAPPOORTEUR)]

OVERVIEW

Regarding the manipulation of science in the toxicity evaluation of glyphosate, much has already been said: the Monsanto papers¹, the copy/paste affair from the dossier into the RAR² and other incidents³ show that industry has largely influenced the analysis of available science in the dossier to guarantee the approval of its pesticide product for market use. In commissioning this report, Générations Futures and PAN Europe wanted to find out how studies showing negative effects of glyphosate are wrongfully (unscientifically) dismissed during the pesticide safety evaluation procedure. For this reason, a consultant was hired⁴ to conduct an independent analysis of the Risk Assessment report on glyphosate. The results reveal that animal studies that report adverse effects following exposure to glyphosate in four categories of toxicity (genotoxicity, carcinogenicity, toxic to reproduction and endocrine disruption) are repeatedly dismissed from the risk assessment procedure of glyphosate without a valid scientific argument being provided.

¹ [The Monsanto Papers: MDL Glyphosate Cancer Case Key Documents & Analysis](#)

² The Guardian: [EU report on weedkiller safety copied text from Monsanto study](#)

³ Open Letter to Commissioner Andriukaitis: Manipulation of science in the glyphosate dossier http://www.pan-europe.info/sites/pan-europe.info/files/20170921_Letter_Comm_Andriukaitis_manipulation_of_science_.pdf

⁴ Tony Tweedale, (M.S). R.I.S.K. (Rebutting Industry Science with Knowledge) Consultancy. Brussels, Belgium.

INTRODUCTION

Pesticide risk assessment (RA) is a pre-market procedure done on the pesticide active ingredient to evaluate its 'safety' when used as a pesticide in order to authorize or re-authorize the placement of the substance on the market. Since 2009, pesticide RA in the European Union (EU) must include *all available data*, including the last 10 years of the peer-reviewed public scientific literature on the pesticide active substance⁵ (in force since 2012). A previous Pesticide Action Network Europe (PAN-E) report⁶ showed that pesticide manufacturers and their regulators are largely ignoring this mandate, identifying on average (in seven randomly selected RAR) only 25% of the easily found toxicity studies from the scientific literature (some, zero). None of these studies are used for final risk assessment, rather they are generally dismissed due to various reasons, including not being done according to OECD-protocols (using the 'Klimisch' ranking, invented by BASF employees) and avoiding in this way the burden of reading and assessing the quality of the *inconvenient* findings.

A RAR - on which the EU Commission's decision to authorize or not a pesticide active ingredient is based- is generated through close collaboration between the industry applicant and the government regulator - in the EU, the Rapporteur Member State (RMS), is usually the relevant authority (e.g. chemical or health agency) of an EU-assigned country. Industry delivers all required data (physio-chemical properties, exposure, metabolism, food residues, toxicity, ecologic toxicity) and recommends conclusions about risks following exposure scenarios; the RMS evaluates this, asks questions, gets more data, and makes its own conclusions. This takes at least one, typically two years (depending on how old and studied the pesticide is), and *only then* are public comments accepted through a public consultation process. After a peer-

⁵ Regulation 1107/2009, Art.8.5: "Dossiers, The summary dossier shall include the following: Scientific peer-reviewed open literature, as determined by the Authority, on the active substance and its relevant metabolites dealing with side-effects on health, the environment and non-target species and published within the last 10 years before the date of submission of the dossier shall be added by the applicant to the dossier."

⁶ [Missed & Dismissed - PAN Europe](#), 2014.

review by the European Food Safety Authority (EFSA) that involves the feedback of Member States and the general public, EFSA delivers its opinion to the Commission. The Commission has then to prepare a proposal in relation to the (re-) authorization of the active substance and present it to the Member States for voting (“Annex 1 authorization”).

RAR and other RAs use the same general format. For pesticide active ingredients, the hazard and exposure assessments and safe dose selections are given in Annex B-6 of all pesticide RARs. The toxicity studies evaluated in that section begin with semi-chronic exposures, then genome toxicity, cancer/general chronic tests, reproductive / developmental exposure (including birth defects), endocrine disruption, neurotoxicity, immunotoxicity, to miscellaneous exposures (other endpoints, veterinary, poisonings). However, in fact the evaluation of many chronic toxic effects (except reproduction and cancer) is hardly possible because there are no mandatory tests for endocrine disruption, immunotoxicity, developmental neurotoxicity and many other serious chronic diseases of humans.

What RAR and other RA contain are summaries of toxicity studies, ranging from a sentence or a phrase to several pages, sometimes with summary charts of the findings. Following each summary there is (not always) the industry's conclusion in relation to the relevance and reliability of the study and the RMS's evaluation (agreement or disagreement). Usually, every endpoint (genotoxicity, carcinogenicity etc.) gets an overall summary.

Most studies are commissioned by the manufacturer to satisfy the requirements of the RA, and they are mostly un-published and non-peer-reviewed, as well as confidential. Since the new EU mandate to also evaluate academic studies, most RARs separate the ones they find in academic literature from their own sponsored studies, and evaluate this literature *en masse*. Crucially, whatever evaluation of the academic literature is done, it occurs after the safe dose has been set, from industry's own toxicity studies. Therefore, the academic literature can hardly influence the conclusions of the report,

even when it provides scientific evidence on adverse effects of the pesticide substance at lower doses⁷.

METHODOLOGY:

This report was commissioned by Générations Futures and PAN Europe to examine how many of the publicly available academia toxicity studies of glyphosate were in fact included in the RAR and how they were evaluated. The overall aim was to investigate the means by which a RAR takes into consideration all toxicity findings, as requested by European law (Article 8, 1107/2009). In a previous work in 2014⁸, a search was conducted into PubMed (a database of almost all published papers in biology, medicine, toxicology and other scientific disciplines) and a total of 146 published toxicity studies reporting adverse effects following glyphosate exposure were found. The RAR⁹, however, found only 51% (76 studies) of these, of which only 24 were discussed (evaluated) in any way (even with just a phrase or a sentence)¹⁰. In addition to the 70 published toxicity findings which the RAR completely failed to report, some of the remaining studies (approx. 50), as well as some studies from industry that showed adverse effects, are simply not evaluated at all. A few hundred more toxicity studies performed by industry were evaluated in the RAR, but here we analyze only those that were given a specific scientific reason to be dismissed. The present analysis, therefore, was designed to examine in detail those 24 academic studies as well as a few industry-sponsored studies reporting adverse effects due to glyphosate exposure that were included in the RAR but were dismissed from the final safety

⁷ Note how neither the full study or the raw data of the industry submitted to the RMS are available to the public, including academic researchers. This report is based only on the publicly available summaries of industry and RMS, and therefore cannot assess whether all toxicity findings are properly evaluated and included in the summary and what is the actual scientific quality of the studies. The only exception is the two key chronic toxicity studies from which the proposed safe dose derives, that were just released by EFSA (only the result tables and individual animal data were released, not their narrative introduction, results, discussion and conclusion).

⁸ PAN Europe, 2014. "Missed and dismissed"

⁹ Renewal Assessment Report Volume B-6 (toxicology) publicly available at: <http://dar.efsa.europa.eu/dar-web/provision>

¹⁰ this is a significantly lower number of studies compared to other pesticide RARs

evaluation of glyphosate and the reasons under which they were dismissed. We selected in total 16 reasons for dismissal that have been detected in other pesticide dossiers, during a previous study.

RESULTS AND DISCUSSION¹¹

In all the studies examined (that includes academic studies reported in the RAR and industry-sponsored studies showing adverse effects following glyphosate exposure that were dismissed from the final evaluation of glyphosate safety) a total of 49 cases were evaluated where reasons for dismissal were provided (some studies report more than one adverse effect, therefore have more than one reason to dismiss; when similar, the different reasons to dismiss were grouped into one).

A detailed summary of our evaluation of each glyphosate toxicity study dismissed for an apparently 'scientifically'-specified reason (other than acute toxicity and ecotoxicity), whether performed by industry or by academia, is shown in the following.

¹¹ Page numbers in this section refer to Vol. B-6 (toxicology) of the public version of the RAR. 16 categories of reasons to dismiss were collected, but the list below is organized by toxicity endpoint. A '| |' mark below separates our summaries of either: different studies in the same category of reasons, or a second reason in the same category. Generally, dismissals of these formulation findings (incl. all epidemiology disease associations) are not here evaluated, as it is true that the toxicity of a mixture cannot be simply ascribed to one component. Under EU law, formulations are assessed by individual countries (never properly done, e.g. the potent ED).





Glyphosate RAR's Reasons to Dismiss Toxicity Findings

Dismissal Category/ Toxicity endpoint examined	<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>	<u>7</u>	<u>8</u>	<u>9</u>	<u>10</u>	<u>11</u>	<u>12</u>	<u>13</u>	<u>14</u>	<u>15</u>	<u>16</u>	<u>Total</u>
Genotox	2	2			1						2	1	2		2	3	15
Cancer		2					1			2		1	1				7
Reprotox							1					1	1		1		4
Developmental	1	1					1	2				1	1		2	1	10
Endocr. Disrptn.	1								1		1	1					4
Other		1	1	1		1		1	1	1		1			1		9
<u>TOTAL</u>	4	6	1	1	1	1	3	3	2	3	3	6	5	0	6	4	<u>49</u>

Reasons to Dismiss (the most commonly used reasons in bold):

1. Not replicable / ignores Weight of Evidence (coherence, consistency)
2. **Not according to Test guidelines, GLP (e.g., Klimisch criteria)**
3. Not treatment related (no further explanation)
4. Non relevant for humans
5. Systemic toxicity (including changes in substance excretion)
6. Adaptation to toxicity
7. Not a toxic effect, per se
8. Not statistically significant / underpowered so unreliable
9. Not in vivo
10. Inadequate route of exposure (evades liver metabolism & excretion)
11. Agent purity is not tested
12. **Ignores effects in some organs**
13. **'historical' control group showing high toxicity in the same range as the exposed group even though concurrent control group showed no toxicity**
14. Lacked a positive control (aids sensitivity)
15. **Non linear dose-response relation**
16. Wrong or unknown mechanism

Classification of Reasons to Dismiss in 4 color-coded categories according to level of rationality (logic):

Some or All Good Logic	4	
Poor Logic	11	
Mostly Illogical	18	
Preposterous Logic	16	

Total Irrational dismissals 45 of 49

An interesting finding is that by using such scientifically ‘vague’ Reasons to Dismiss (RtD) or misusing other RtDs, industry is dismissing many of *its own* findings of toxicity, especially *at relatively low dose studies* (note how frequently a finding is dismissed for not increasing as the dose increases (reason 15). In fact, life needs to use low dose signals (molecules are biologically active at very low doses) and effects of chemicals at low doses are very relevant during their safety assessment. Accordingly, there are already about 8,000 published toxicity findings of low dose toxicity of chemicals in vertebrates. In contrast, industry's Test Guideline (chronic toxicity) methods are designed to detect only the end of poisoning, yet are used to detect chronic exposure toxicity.

We only evaluated the cases where a scientific rationale was given, and in these cases it is remarkable that almost every *sentence or phrase in the RAR* used to dismiss a study is literally scientifically unfounded. Historical controls, although they can increase the statistical power of studies when used correctly, in the RAR of glyphosate they are clearly being used to mask inconvenient findings of low dose toxicity (as they are not validated and are included only in industry's secret databases).

Such constant, sweeping dismissal of findings, the missing of many important ones, and the failing to evaluate others at all, means that important and often replicated studies of hazardous effects on mammals, such as humans, will certainly lead to a lack of protection of the public against the harms of synthetic pesticides. There are simply

too many findings of toxicity below the dose that is claimed to be the lowest no-effect dose for glyphosate in the world - and too many findings were not evaluated. This reveals once again that the evaluation of glyphosate hasn't been done correctly so it could be re-authorized.

ESPECIALLY FLAGRANT DISMISSALS

Example Dismissal 1, Toxicity at low dose

Considering that industry excoriated the academic Séralini laboratory for reporting excess RoundUp toxicity in an apparently 'underpowered' study, this earlier industry study provided below is an example of a much worse design. Not only it used small number of animals per group, but the organs of the low- and mid-dose animal groups were not even microscopically analyzed.

No stated reason was given, but it remains unclear whether a significant toxicity was detected during the gross examination of animals at the two lower doses, leading to the decision not to analyze the organs at these doses. Actually this 1981 Monsanto study is the only one using such a low dose range.

To compound the error, RMS rejected it for using too low a range of doses. The scientifically correct response to the assumed problem of the dose being too low to elicit enough disease to detect is to increase the group size. This is what the academic Ramazzini Institute is doing in their ongoing glyphosate long-term exposure studies. That is what 'sound' science should really do, and not just to dismiss the study as invalid without repetition.

Example 1 from the RAR's summary of the study (emphasis is given in bold letters):

Pages 574-581:

TOX9552385; IIA, 5.6.1/05; **A three-generation reproduction study in rats with glyphosate**

Data owner: Monsanto Study No.: 77-2063; BDN 77-417 Date: 1981-03-31 (pre-guideline)

p. 575: "...groups of 12 male and 24 female CD rats received beginning 63 days prior to mating of the F0 generation daily dietary **doses of 0, 3, 10 and 30 mg glyphosate/kg bw in diet.** "

(p. 576): Sacrifice and pathology

"... F1a, F2a, F3a and F3b animals were sacrificed at weaning, given a gross post-mortem examination and abnormal tissues were saved. F1b and F2b animals which were not selected as future parents were sacrificed after ensuing selection of parental animals, given a gross post-mortem examination and abnormal tissues were saved. ... **Microscopic examination of histological sections of these tissues were done for 10 male and 10 female animals from control and high-dose groups of F0, F1 and F2 parents and of F3b offsprings.**"

p. 581: "**Conclusion by the Notifiers**

The oral administration of glyphosate to rats by dietary admixture at a maximum dose level of 30 mg/kg bw/day for three successive generations of CD rats resulted in no treatment-related signs of toxicity in parental animals. The NOAEL for reproduction is 30 mg/kg bw/day, since the reproductive performance was not affected in any dose group. The NOAEL for offspring is 30 mg/kg bw/day, since no adverse effects on offspring were observed.

Comment by RMS (Re-evaluation):

*This study is now considered **not acceptable due to the selected dose levels that were much too low.** Accordingly, an effect dose was not reached (Evaluation in 2001 not confirmed)"*

Example Dismissal 2: Dueling test methods, Kllimisch score in Genotoxicity assessment

The Test Guideline (TG) methods for genotoxicity require the DNA mutation potential to be tested, mostly in bacterial cells. Academic scientists often test for effects in any aspect of genotoxicity, e.g. chromosome damage, oxidative stress, and *in vitro*, often in more realistic animal cell lines. The RAR calls academia's methods "unreliable" (e.g. p. 377, p. 416) and dismissed all 16 studies that had detected some

type of genotoxicity by assigning them a low reliability Klimisch¹² score of 3 (a literature search also shows there are a few more studies that were never found by the RAR). Ironically, the single negative finding from academia gets a Klimisch 2 score (see p. 420-447).

Example dismissal 3: historical controls.

The study summary in the RAR discloses that historical controls were used in several key studies to dismiss observed adverse effects in exposed animal groups. For example, in one of them (Brooker '91), the rate of implanted fetus loss in the lowest dose group (50 mg/kg per day) was three times that of the unexposed animals (concurrent control). However, RMS accepted industry's evaluation comparing this dose group to their 'unpublished' historical controls that had suspiciously high rates of fetus loss instead of using the concurrent control for comparison. In this manner, glyphosate, conveniently, wasn't showing to cause any effect at all. In reality, the concurrent controls of an experiment are always more pertinent than even the most transparent and carefully curated historic controls. Therefore, that strong toxicity did occur, at the dose that we are told that are perfectly safe.

Beyond these detailed examples, a summary of our evaluation of each dismissed glyphosate toxicity study follows.

¹² The Klimisch score (1-4) is a method of assessing the reliability of toxicological studies with score 1 being reliable without restriction (usually GLP studies) and score 4 being not reliable at all.

TECHNICAL DETAILS¹³

Genotoxicity

Positive human academia findings dismissed for imprecise methods (i.e. not replicable); p. 409-12. || The several positive industry findings on clastogenicity (chromosomal toxicity¹⁴) on active substance and formulations dismissed due to the many more negative industry findings (in ea. subcategory of genotoxicity); as well as for occasional specific reasons too numerous to list here; p. 399-406.

Academia's genotoxicity studies claimed to use “unreliable methods”; p. 377 and 416; Test guidelines is the criterion, p. 371 and 418. All 16 academia positive findings (note, PubMed returns 27) called unreliable due Klimisch score 3 (except a weak epidemiological formulation finding, assigned K2), the one negative academia finding also K 2; p. 420-447. || Alkaline conditions of Comet test claimed to be cause positive findings; var. pp. || New positive industry findings dismissed for not knowing if scoring was blinded; p. 399, 402.

A handful of positive industry mutagenicity findings dismissed for being at cytotoxic dose or other poor methods vaguely noted; p. 402-9.

Dozens of older industry and at least 1 academia positive result, including in humans, ascribed to surfactant potency = cytotoxicity (poisoning) at low dose (illogic); p. 372-390, same for new industry ones p.414-5 (this also ignores the active ingredient's positive genotoxicity findings). Two positive industry, including *in vivo* mammalian, dismissed for using uncommon, uncharacterized formulation; p. 401, 406.

¹³ Page numbers in this section refer to Vol. B-6 (toxicology) of the public version of the RAR. 16 categories of reasons to dismiss were collected, but the list below is organized by toxicity endpoint. A '||' mark below separates our summaries of either: different studies in the same category of reasons, or a second reason in the same category. Generally, dismissals of these formulation findings (incl. all epidemiology disease associations) are not here evaluated, as it is true that the toxicity of a mixture cannot be simply ascribed to one component. Under EU law, formulations are assessed by individual countries (never properly done, e.g. the potent ED).

¹⁴ where substances can cause breaks in chromosomes leading to sections of the chromosomes being deleted, added or rearranged

Industry *in vitro* negative mutagenicity result on glyphosate's major metabolite AMPA was performed pre-incubation of cells only, despite industry claiming otherwise, the Rapporteur member state notes; p. 726.

Industry *in vivo* high dose study finds micronuclei in red blood cells at 600 mg/kg, dismissed by industry as “in range of historical controls”, also saying it is likely due to high dose cytotoxicity; RMS agrees, even though positive control responded same so not likely (p. 357). And as a similar (dismissed) industry positive finding (p. 359) is at low dose (30 mg/kg), it is altogether impossible to be due to poisoning due to high dose (cytotoxicity)! || Ironically, positive industry genotoxicity finding dismissed for not using concurrent control, p. 399!

Rapporteur member state dismissed academic confirmation in humans and by industry of blood cell micronuclei at just 30 mg/kg: “the doses far too low to draw meaningful conclusion” (reality is just the reverse); p. 359 (another industry neg. finding at low dose, Rapporteur member state dismissed for same reason). Rapporteur member state reveals these doses chosen due to an uncited low-dose toxicity findings.

The handful of industry positive mutagenicity findings dismissed for not being classic oxidative DNA damage (or for non-mammal model (except 1); p. 402-9. || Structure-activity analysis of glyphosate molecule indicates no genotoxicity concerns, p. 398. || A following industry positive finding dismissed for unclear genetic reason; p. 399. || Negative carcinogen findings by industry are further proof it is not genotoxic, p. 419.

Cancer

Industry and RMS say a fairly low dose industry study 'no-effect' dose (NOAEL) of circa 30 mg/kg/day is invalid as current tests guidelines require higher doses; p. 473. || Of academia's published epidemiology and animal cancer related studies, most are given a Klimisch score of 3 (one formulation and one negative animal finding get K2 score); though specific (if as usual often illogical) alleged failures are cited; pp. 518-38. || Séralini (academia) tumor finding (formulation) dismissed for not following test guidelines (thus not large enough animal groups; underpowered), given K 3 score; p.

537. Séralini's main (at the time) response is mentioned but was not summarized (it was: too few animals to use statistics, the blood chemical hormones indicating cancer were statistically significantly elevated; and the exposure period was long).

RMS is correct to say effects at the high dose in industry studies merit lowering industry-claimed NOAELs from the high to the mid dose; p. 467, 479, 487, 492.

Academia cancer-promoting effect of formulation dermally applied dismissed by industry as due to local irritation, despite also finding that cancer-related proteins were expressed in treated animals; p. 535 || Industry illogically says that is not a cancerous effect; p. 521-2.

Rapporteur member state approves of industry ignoring blood chemical changes in industry study at NOAEL *~12x lower than the alleged lowest no effect level for the safe dose*; p. 452. || Salivary toxicity earlier found by same lab ignored by industry; p. 460.

RMS instructs industry to use historical instead of concurrent negative controls (but at least says the agreed 150 mg/kg/day NOAEL of a study should be based on possible increase in cancer, not on non-cancer effects; p. 501-2).

Reprotoxicity¹⁵

High dose industry study, RMS dismisses F1 generation lack of pregnancies at mid dose because they later were able to mate untreated rats; p. 566.

Low dose industry: microscopic analysis of organs at 30 mg/kg/day animals not performed at 3 and 10 mg/kg/day! (p. 576).

RMS agrees with industry: often significant decreases in mating, pregnancy and litter viability across all generations and doses in industry at moderately low dose study

¹⁵ Note: developmental and reprotoxicity (DaRT) and endocrine disruption (ED) studies were analyzed in RAR together (per COM's interim ED criteria), except ED also analyzed separately...but in ecotoxicity chapter of the RAR! See separate critique of industry poor supplementary (2015) ED literature review after COM asked for it.

(3/10/30 mg/kg/day) are due to unusual rates in negative controls (and to non-linear dose response); p. 578-9.

RMS agrees with industry that significant reduced litter size in F0 and F1, and male reproductive organ damage in offspring (F1) are not repeated at 10 and 100 X the dose, so must not be real; p. 573-4. Rapporteur member state says all doses in industry low dose study too low to be valid; p. 585.

Developmental / Teratogenicity

High dose industry study rejected by RMS for many reasons including no statistical analysis and failing to analyze for effects, and for reporting toxicity that wasn't when the study was presented at last authorization.; p. 654 (evaluation poorly done, total lack of detail).

Academia formulation toxicity to frog and chicken eggs dismissed as irregular direct exposure method, p. 559.

Highly significant rabbit rib and skeleton malformed at mid dose only in an industry fairly low dose study undiscussed by both industry and Rapporteur member state; p. 613.

Fairly consistent heart defects across all doses (low: 20 mg/kg/day) in low dose industry study: small groups and no Dose Response cause Rapporteur Member State to dismiss them (but Rapporteur member state rejected industry argument for an even higher NOAEL), saying industry claim of "gavage error" simply untrue; p. 651). || Paid consultant published review of industry studies claiming no heart defects; p. 659 (a contradiction to studies in RAR, though parties claim not).

Rib defect at high dose ignored by industry in high dose industry study, so Rapporteur member state says NOAEL is at mid dose; p. 607.

RMS: mid dose cardiac and other defects implied to vanish if use industry's historic controls on industry test; p. 647. || Rib defects at high dose in industry study dismissed as less than historical control rate; p.651.

Highly significant pregnancy failure rate at low dose in industry high dose study dismissed by industry and Rapporteur member state as mostly not occurring at highest doses; p. 603. || Academia dismissed (ironically) for unrealistically high dose; p. 559.

RMS denies industry NOAEL of 200 mg/kg/day, sets it at 50 mg/kg/day, as industry did not propose mechanism to explain their reason to dismiss (early fetal death); p. 619-21.

Endocrine Disruption

Bizarrely, published experimental data showing various Endocrine Disruption effects dismissed for being the published data of another laboratory; p. 659.

Academia findings of hormone receptor mediated cell proliferation dismissed for being *in vitro*, while industry *in vivo* studies for Endocrine Disruption were negative (but this ignores other positive findings); p. 559.

Formulation findings, ~ 8 positive *in vitro* and *in vivo* Endocrine Disruption (one reprotoxicity), and academia positive findings on glyphosate all 'unreliable' Klimisch 3, w/ too many other flaws listed to critique here (but similarly illogical to those that are); p. 663-79.

Rapporteur member state apparently agrees with industry saying hormonal "activity", whether just biochemical or final effect, can be detected by industry's high dose (insensitive) Test Guidelines reprotoxicity test methods; p. 597.

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