University of Sussex

Prof Erik Millstone
SPRU- Science and Technology Policy Research
Freeman Centre, Jubilee Building
University of Sussex
Brighton BN1 9SL
England

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Dear Sir/Madam

Re. comments on the February 2015 EFSA/WHO DRAFT for public consultation on a possible *Threshold of Toxicological Concern Approach: Conclusions and Recommendations of the EFSA/WHO Expert Workshop*

Executive Summary

The text provided by the EFSA/WHO draft fails the tests for transparency that EFSA set in 2009 in the *Guidance of the EFSA Scientific Committee on transparency in the scientific aspects of risk assessment carried out by EFSA. Part 2: general principle*.[1] The detailed requirements of that guidance are set out below, but the draft text on a *Threshold of Toxicological Concern Approach* fails to meet several of those requirements.

The EFSA guidance stipulated that "All assumptions should be documented and explained." [and] "Where alternative assumptions could reasonably be made, the related uncertainties can be evaluated together with other uncertainties…" Numerous assumptions remain unacknowledged in the draft text, which contrives to avoid addressing the implications of questioning those assumptions or of making other assumptions that could provide significantly higher standards of protection for public health.

The draft treats improvements in the sensitivity of analytical testing technologies as a threat to the *status quo* rather than as an opportunity to improve the protection of public health. The EFSA/WHO draft's narrative presupposes a set of assumptions that are antithetical to precaution and inappropriate for bodies supposed to take responsibility for protecting public health. The implicit assumptions effectively assign a higher priority to the commercial interests of the food and chemical industries than they do to the protection of public health.

EFSA's guidance that: "If data are excluded, this should be stated along with the rationale for their exclusion" has not been complied with. Some criteria of inclusion and exclusion are explicit, while many others are implicit, but the choice of those criteria has not been explained let alone justified. Readers are told something about considerations that have not been included, but no explanation or justification for excluding those considerations is

[1] *The EFSA Journal* (2009) 1051, 1-22

contact us

Prof Erik Millstone
Professor of Science Policy

SPRU
Freeman Centre, Jubilee Building
University of Sussex, Brighton
BN1 9SL United Kingdom

T +44(0) 1273 877380
F +44(0) 1273 685865
e.p.millstone@sussex.ac.uk
www.sussex.ac.uk

provided. The EFSA/WHO draft selectively invokes some data sets, but not others, yet fails to justify the selection or the exclusions. EFSA guidance recommends that all relevant data should be "…evaluated to determine their quality and relevance to the assessment." Instead, in this draft, those that are convenient are reported as if entirely unproblematic, while inconvenient data and questions are ignored or discounted.

Chronic uncertainties in the studies and databases that are included are not acknowledged, their relative weakness is not taken into account and no overall evaluation of uncertainty is provided. The draft conclusions and recommendations presuppose evaluative judgements, but the text is drafted in the rhetorical guise of factual statements, a tactic that also fails to comply with EFSA's stipulated guidance.

The EFSA/WHO draft on a possible *Threshold of Toxicological Concern Approach*, and the concept of a TTC itself, are un-scientific and anti-scientific. They are un-scientific because they constitute thinly-disguised corporate wishful thinking masquerading as if they are providing estimates of natural constants. They are anti-scientific because they are being invoked as grounds for not requiring firms to conduct or commission toxicological tests. The draft proposes to rule out *a priori* entire ranges of investigations; such studies are supposedly unnecessary as the authors of the draft document pretend that they already know what the results will show. While the idea of a TTC could be treated as a hypothesis for testing; using it as an excuse for insisting that no tests should be conducted is irredeemably anti-scientific.

The EFSA/WHO draft therefore does not provide a satisfactory basis for policy-making in EFSA or at the WHO.

Introduction

The following comments on the February 2015 EFSA/WHO DRAFT for public consultation on a possible *Threshold of Toxicological Concern Approach: Conclusions and Recommendations of the EFSA/WHO Expert Workshop* are informed in large part by two other documents. In this document, as in many others, the expression 'threshold of toxicological concern' will often be abbreviated as 'TTC'.

One of those documents was issued in April 2009 by EFSA. It was entitled *Guidance of the EFSA Scientific Committee on transparency in the scientific aspects of risk assessment carried out by EFSA. Part 2: general principles* in response to Question No EFSA-Q-2005-050Ba, and adopted on 7 April 2009.[2] That document set several minimum standards that should be satisfied by any and all EFSA risk assessments. It is important in this context because the EFSA/WHO document on a TTC fails to satisfy those requirements, and therefore it does not form a satisfactory basis for any EFSA policy decisions about the utility or acceptability of the concept of a TTC.

The second document, by reference to which the EFSA/WHO draft on a TTC will be appraised, is a presentation made by the Canadian scholar Professor Heather Douglas to the first conference of the International Network for Government Scientific Advice, which was held in August 2014 in Auckland, New Zealand. (See http://globalscienceadvice.org/) Douglas there set out five phenomena, or 'patterns of argument' that individually and severally provide indicators of 'a lack of integrity' on the part of science advisors to public policy-makers.[3]

EFSA's benchmarks of transparency

EFSA's April 2009 document stipulated that: "…scientific outputs must be transparent with regard to the data, methods of analysis and assumptions that are used in the risk assessment process…

- ***Transparency is needed in all parts of the risk assessment***…
- *To be transparent, a risk assessment should be understandable and* ***reproducible…***
- ***The sources of all data*** used for the assessment, including unpublished data and personal communications, ***must be referenced and…evaluated to determine their quality and relevance to the assessment***. ***These should be reflected in the relative weight given to them in the assessment and taken into account in the overall evaluation of uncertainty***…
- The inclusion/exclusion criteria applied to the data should be explained and described within the risk assessment. ***If data are excluded, this should be stated along with the rationale for their exclusion***." …
- ***All assumptions should be documented and explained***. Where alternative assumptions could reasonably be made, the related

[2] *The EFSA Journal* (2009) 1051, 1-22

[3] H Douglas, 'Science and Citizens', conference presentation to www.globalscienceadvice.org 23 July 2014, available at http://www.slideshare.net/sciadvice14

uncertainties can be evaluated together with other uncertainties…" (emphases added)[4]

While some might question whether that guidance should be deemed applicable to the EFSA/WHO document on a TTC, the working group itself claims (lines 9-10) that: "the TTC approach integrates data on exposure, chemical structure, metabolism, and toxicity consistent with standard risk assessment principles." It therefore follows that the draft document on a TTC can appropriately be judged by reference to the criteria required by EFSA for genuine transparency.

Declarations of interests and confidentiality

The text states (lines 37-40) that: "The experts completed a declaration of interests and a declaration of confidentiality that were evaluated by WHO according to the organisations' rules. WHO concluded that the interests declared did not warrant experts to be excluded from the discussion at the meeting." That only indicates that the declarations were benchmarked by reference to WHO requirements, but it does not indicate how the EFSA rules on conflicts of interests might have been applied or interpreted. This is important because the WHO's rules are weaker than those of EFSA; indeed some might say 'even weaker'. The comment about '…declarations of confidentiality…' appears moreover to conflict directly with EFSA's requirement for transparency, since transparency and confidentiality are mutually exclusive.

Scope and limits of relevant considerations

Readers are told (lines 95-101) that: "There are generic questions in the risk assessment of chemicals that are under discussion in the scientific community, sometimes for decades (e.g. the existence of a toxicological threshold dose below which no adverse effect is produced, low-dose effects due to non-monotonic dose-response relationships, mixtures, interspecies extrapolation, adequacy of endpoints tested, fetal origin of adult disease, epigenetics, dose-metric, extrapolation from subchronic to chronic studies, endocrine disruption). Such questions apply also to the TTC approach but are not specific to it and discussion on such generic risk assessment considerations are not in the scope of this report."

It is true that those considerations were omitted from the draft text, a fact that is difficult to reconcile with the fact that precisely those considerations were explicitly raised during the workshop on the TTC held by EFSA and the WHO in Brussels on 2nd December 2014. Furthermore the bald statement that such considerations were deemed, by the drafting team, to be beyond the scope of its deliberations, is incompatible with EFSA's stipulation that: "The inclusion/exclusion criteria applied to the data should be explained and described within the risk assessment. ***If data are excluded, this should be stated along with the rationale for their exclusion***… ***All assumptions should be documented and explained***. Where alternative assumptions could reasonably be made, the related uncertainties can be evaluated together with other uncertainties…"

[4] Guidance of the EFSA Scientific Committee on transparency in the scientific aspects of risk assessment carried out by EFSA. Part 2: general principles. in response to Question No EFSA-Q-2005-050Ba, and adopted on 7 April 2009, *The EFSA Journal (2009)* 1051, 1-22

The draft TTC document provides no rationale for excluding those considerations from its scope; we are only told that they were excluded, as if that assumption was unproblematic and as if alternative assumptions were not available, when clearly they were.

The decision to ignore or discount all of those considerations clearly favours the commercial interests of the food and chemical industries and was correspondingly antithetical to the protection of public health. If issues such as "…non-monotonic dose-response relationships, mixtures, interspecies extrapolation, adequacy of endpoints tested, fetal origin of adult disease, epigenetics, dose-metric, extrapolation from subchronic to chronic studies, [and] endocrine disruption…" were to be taken into consideration, then familiar narratives suggesting that all food-borne toxicological risks are already being adequately and properly regulated could lose their plausibility. The EFSA/WHO draft TTC text presupposes an assumption for which no explanation was provided, and which favours corporate interests while potentially compromising the protection of public health.

The EFSA/WHO draft suggests (line 71) that one key question is: "Is the TTC concept based on scientific risk assessment principles and sufficiently conservative for public health protection?" But the text never identifies the implicit criterion of 'sufficiency', nor for whom sufficiency is being judged? Judgements as to benchmarks of 'sufficiency' are not themselves purely scientific judgements, they are normative and evaluative judgements, which in the TTC draft remain entirely implicit. That fails to comply with EFSA's stipulation to the effect that '…All assumptions should be documented and explained. Where alternative assumptions could reasonably be made, the related uncertainties can be evaluated together with other uncertainties…"

The very start of the TTC draft (lines 2-3) reveals that a central concern behind the initiative to have the concept of a TTC officially endorsed has arisen primarily because of "…ever improving methods in analytical chemistry, [so that] it is to be expected that many more unintended chemicals will be detected in…food and drinking water, as well as in our bodies." Instead of responding to that improvement in the sensitivity of scientific instrumentation as an opportunity to enhance the protection of public health, it is being treated as a threat to the *status quo* and to the commercial interests of the chemical and food industries. If the primary focus of the EFSA/WHO drafting team had been on the protection of public health the resultant text would have welcomed the improvement in the sensitivity of chemical analyses.

The Cramer, Ford & Hall scheme

Section 3.2 of the EFSA/WHO TTC draft boldly asserts (line 134) that "*The Cramer scheme is fit for purpose*", but the assumptions underlying the construction of that approach were not acknowledged when the scheme was first proposed in 1978, nor are they recognised or justified in the EFSA/WHO TTC draft. In a document such as this, a mere assertion that the Cramer scheme is fit for purpose provides a very poor substitute for a proper justification, especially in light of the fact that the Cramer, Ford & Hall scheme is profoundly problematic when judged from the perspective of the protection of public health .

The FEMA Decision Tree

In 1978 Cramer, Ford and Hall (two of whom worked for the Flavor and Extracts Manufacturers Association of the United States (or FEMA) and the third worked closely with FEMA) purported: "…to formalize the relationship of chemical structure and the level

of use (and importance) to the estimation of toxic hazard…"[5] Their approach was adopted by FEMA, and implicitly accepted by the US FDA and subsequently refined in terms of a 'decision tree', which has been used by JECFA and EFSA. That decision-tree was based upon the 3-fold typology of what were alleged to be 'structural classes', and modulated in terms of estimates of levels of exposure. Cramer, Ford and Hall claimed that their decision tree was not intended as "…a substitute for data but [a] guide to the priority and scope of the effort required to acquire more information".[6] But that was disingenuous because it has subsequently been interpreted and used by the FEMA Panel and by WHO and EFSA panels as precisely that: as ground for not requiring tests, and therefore as a substitute for toxicological data.[7] The proposed TTC figures, and the entire apparatus involved in assuming that TTC's can be robustly established, constitute as exercise in corporate wishful thinking, in which figures masquerade as if they were empirical findings. The TTC figures are not robustly evidence-based but constructed by combining modest amounts of data with sweeping and optimistic general assumptions about the similarities in the metabolic pathways of groups of chemicals which share some common features. The absence of conclusive evidence of risks (inevitable if tests are not required) is misrepresented as if providing reliable evidence of the absence of any risks.

The FEMA Panel, and now the EFSA/WHO drafting team did not quite pull TTC figures out of the air, they did assemble a data base, but included modest numbers of relatively superficial, outdated and insensitive studies. Moreover, their judgements as to how much or how little evidence they would consider acceptable and sufficient were arbitrary and unscientific; they are also favourable to the food processing and chemicals industries and antithetical to the interest of consumers. The EFSA/WHO team treats TTC figures as if they were accurate estimates of natural constants, which had been established empirically as biochemical thresholds, rather than as their chosen levels for expressing their collective concern. Those judgements were, and remain, subjective; they are not scientific.

Sufficient evidence and sufficient protection?

The EFSA/WHO TTC draft (line 231, section 3.5) asserts that: *"The TTC for Genotoxic compounds is sufficiently protective"*, but as the text acknowledges (lines 236-7): "The values in the CPDB database are derived assuming linearity of the dose response curve by extrapolation from the lowest TD50 for each chemical." But linearity is not an especially conservative assumption, and the document fails to justify that assumption or explain why it was adopted. Nor does it acknowledge that other plausible assumptions are available, let alone explore the implications of selecting amongst the alternatives.

Section 3.7.1 of the EFSA/WHO TTC draft acknowledges that the database on which the TTC figures have been based is incomplete, and in particular has little information on non-cancer effects, especially (line 282) 'reproductive and developmental toxicity'. The document comments (lines 276-283): "If a new non-cancer database is generated, then the 'overall TTC's' should be recalculated…Should the recalculated TTC values for the

[5] R L Smith et al, 'Criteria for the safety evaluation of flavoring substances: The Expert Panel of the Flavor and Extract Manufacturers Association', *Food Chemical Toxicology*, 2005, Vol 43, 1141-1177; referring to G M Cramer, R A Ford & R L Hall, 'Estimation of toxic hazard—a decision tree approach', *Food and Cosmetic Toxicology*, 1978, Vol 16, 255–276

[6] G M Cramer, R A Ford & R L Hall, 'Estimation of toxic hazard—a decision tree approach', *Food and Cosmetic Toxicology*, 1978, Vol 16, 255–276

[7] Robert L. Smith et al, Criteria for the safety evaluation of flavoring substances The Expert Panel of the Flavor and Extract Manufacturers Association, *Food Chemical Toxicology* , 2005, Vol 43, 1156-1157

respective classes increase, it needs to be determined if the new TTC values can still be considered sufficiently protective for adverse effects on specific endpoints, such as reproductive or developmental toxicity, as has been demonstrated for current TTC values."

The draft TTC document fails to explain why the current approach should be deemed adequate given that it currently does not include all the potentially available data. It is also unscientific to suggest that the currently proposed 'TTC values' have been 'demonstrated' to be sufficiently protective. Given the incompleteness and equivocality of the available data, and the number of unacknowledged and undefended assumptions in the draft document, it is misleading to pretend that any such demonstration has been provided, especially as no criterion of sufficiency is given, let alone justified.

Obfuscations and ambiguities, but not transparency

Section 3.7.2 (lines 298 to 309) provides an interesting example of obfuscation and the exploitation of ambiguity; which are of course antithetical to transparency. The relevant passage starts by implying that the TTC approach is a type of risk assessment, when it is in fact used as an excuse for not requiring sufficient data of the sort that would be required if a remotely adequate risk assessment were to be conducted. While Meek et al may have indicated: "…how TTC values could be used as the hazard point of departure for groups of substances belonging to specific Cramer classes…" Meek et al did not establish that they *should* be so used. Nonetheless; the document implicitly infers 'should' from 'could', but that is not a legitimate inference.

Given, moreover that an: "…EFSA project on low-dose effects and non-monotonic dose-response…" is still underway, it is premature for the EFSA/WHO panel to presume that, in the meantime, the current proposal is satisfactory. The document fails to explain why it would not be more appropriate and satisfactory to delay any conclusion or recommendation until after the EFSA project on low-dose effects and non-monotonic dose-response has been completed, published and peer-reviewed in a transparent fashion.

In section 4.5 (lines 429 to 442) the document asserts that: "The inclusion of sub-chronic studies in the non-cancer database is supported, and when extrapolating from subchronic to chronic study duration in rodents the group finds the current extrapolation factor of 3 is appropriate for a screening tool." There is however nothing in the antecedent text to explain either where that 'factor of 3' might have come from, or why it might be appropriate. Even less are we told which assumptions underpin that suggestion.

The next paragraph (lines 440-442) states that: "The expert group acknowledged that expressing TTC values on a molar basis may have greater scientific rigour, but recommended maintaining the units in µg/kg bw/day for greater consistency with other health-based guidance values." The document provides no reasons why 'consistency' with what are in practice bureaucratic artefacts is more important than 'scientific rigour'.

Indicators of a lack of integrity

The second document, by reference to which the EFSA/WHO draft on a TTC can be appraised, is Douglas' specification of five phenomena or 'patterns of argument' that individually and severally provide indicators of 'a lack of integrity' on the part of science

advisors to public policy-makers.[8] To the extent that there may be a lack of integrity, it will be important to ask which interests have been served by that lack of integrity and which interests have been compromised?

Douglas explains that if the text of a document:

- ignores inconvenient evidence
- cherry-picked evidence,
- depend on flawed evidence,
- showed no ability to imagine (let alone engage with) evidence that could change their judgements, and
- failed to respond to criticisms,

then there would be good grounds for concluding that scientific integrity had been compromised.

There is evidence that the EFSA/WHO TTC draft text conspicuously displays examples of each of those indicators, which collectively provide robust evidence of a lack scientific integrity. The statement cited above (lines 95-101) that: "There are generic questions in the risk assessment of chemicals that are under discussion in the scientific community…e.g. the existence of a toxicological threshold dose below which no adverse effect is produced, low-dose effects due to non-monotonic dose-response relationships, mixtures, interspecies extrapolation, adequacy of endpoints tested, fetal origin of adult disease, epigenetics, dose-metric, extrapolation from subchronic to chronic studies, endocrine disruption…Such questions apply…to the TTC approach but are not specific to it and discussion on such generic risk assessment considerations are not in the scope of this report..." is a clear example of ignoring inconvenient evidence.

The evidence that is cited in the EFSA/WHO draft is confined to those contributions to the literature that favour the conclusion that was reached. Evidence that would challenge the conclusions, for which the food and chemical industries and their representatives have been calling, has been discounted or ignored. A list of some 36 of the studies that have provided evidence to challenge the assumptions underlying the acceptance of the concept of a TTC, including non-monotonic dose-response relationships, is given at the end of this document in Appendix 1.

Evidence was therefore cheery-picked, rather than comprehensively and objective reported and appraised, in the EFSA/WHO TTC draft. Flaws in the quality of the evidence and limitation to its quantities were not properly reported or evaluated, instead the shortcomings of the incomplete database initially constructed by Cramer, Ford & Hall were glossed over, and the available (convenient) data were portrayed as if sufficient and reliable.

It was striking that, during the meeting in Brussels on 2nd December convened to discuss this topic, and a preliminary document, a group of critics commented directly on the claims that had been made, and articulated relevant and powerful arguments against the proposals. The speakers and participants who defended the draft failed conspicuously to engage with the counter-arguments that the critics had articulated. It was, moreover, striking that one pro-TTC participants in the 2nd December 2014 Workshop explicitly insisted that the

[8] H Douglas, 'Science and Citizens', conference presentation to www.globalscienceadvice.org 23 July 2014, available at http://www.slideshare.net/sciadvice14

meeting should not engage with the substance of the critics' arguments, thereby revealing a unwillingness to imagine or engage with 'evidence that could change their judgements. Those tactics correspond to the fourth and fifth of Douglas' indicators.

Given that the EFSA/WHO draft, and its defenders, have:

- ignored inconvenient evidence,
- cherry-picked evidence,
- depended on flawed evidence,
- showed no ability to imagine or engage with evidence that could change their judgements, and
- failed to respond to criticisms,

an objective commentator might consider whether that constitutes sufficient evidence of a lack of integrity, or if not to ask what other explanation for those shortcomings might be more plausible.

Conclusions

The text provided by the EFSA/WHO draft fails the tests for transparency that EFSA set in 2009 in the *Guidance of the EFSA Scientific Committee on transparency in the scientific aspects of risk assessment carried out by EFSA. Part 2: general principle*.[9] The draft text on a *Threshold of Toxicological Concern Approach* fails to meet the requirements provided by the *Guidance*.

The EFSA guidance stipulated that "All assumptions should be documented and explained." [and] "Where alternative assumptions could reasonably be made, the related uncertainties can be evaluated together with other uncertainties…" Numerous assumptions remain unacknowledged in the draft text, which contrives to avoid addressing the implications of questioning those assumptions or of making other assumptions that could provide significantly higher standards of protection for public health. The draft treats improvements in the sensitivity of analytical testing technologies as a threat to the *status quo* rather than as an opportunity to improve the protection of public health.

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[9] *The EFSA Journal* (2009) 1051, 1-22

Chronic uncertainties in the studies and databases that are included are not acknowledged, their relative weakness is not taken into account and no overall evaluation of uncertainty is provided. The draft conclusions and recommendations presuppose evaluative judgements, but the text is drafted in the rhetorical guise of factual statements, a tactic that also fails to comply with EFSA's stipulated guidance.

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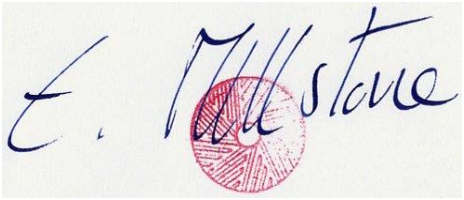
The EFSA/WHO draft therefore does not provide a satisfactory basis for policy-making in EFSA or at the WHO.

Yours faithfully



Professor Erik Millstone

Email: e.p.millstone@sussex.ac.uk
Telephone: +44 (0)1273 877380

Appendix 1: Studies that provide evidence of non-monotonic dose-effect relationships that have been omitted from, and ignored, by the EFSA/WHO drafting team, and by the Cramer, Ford & Hall approach

1. De-Oliveira A C A X, Poca K S, Totino P R R, Paumgartten F J R, 'Modulation of Cytochrome P450 2A5 Activity by Lipopolysaccharide: Low-Dose Effects and Non-Monotonic Dose-Response Relationship', *PloS One*, 2015, Volume:10, Issue:1, Pages:e0117842, DOI:10.1371/journal.pone.0117842

2. Christensen K, Christensen CH, Wright JM, Galizia A, Glenn BS, Scott CS, Mall JK, Bateson TF, Murphy PA, Cooper GS & Glinda S 'The Use of Epidemiology in Risk Assessment: Challenges and Opportunities', *Human And Ecological Risk Assessment*, 18 Aug 2015, Volume: 21 Issue: 6 Pages: 1644-1663 DOI: 10.1080/10807039.2014.967039

3. Freitag AR, Thayer LR, Leonetti C, Stapleton HM, Hamlin HJ, 'Effects of elevated nitrate on endocrine function in Atlantic salmon, *Salmo salar*', *Aquaculture*, Jan 2015, Vol 436 Pp 8-12, DOI: 10.1016/j.aquaculture.2014.10.041

4. Lagarde F**,** Beausoleil C**,** Belcher SM**,** Belzunces L P**,** Emond C**,** Guerbet & Rousselle C, 'Non-monotonic dose-response relationships and endocrine disruptors: a qualitative method of assessment' *Environmental Healt**h*** 2015, 14:13 doi:10.1186/1476-069X-14-13

5. Erofeeva EA, 'Dependence of Dandelion (*Taraxacum Officinale Wigg*) Seed Reproduction Indices on Intensity of Motor Traffic Pollution', *Dose-Response*, 2014, Volume: 12, Issue: 4, Pages: 540-550, DOI: 10.2203/dose-response.14-009.Erofeeva

6. de Cock M, van de Bor M, 'Obesogenic effects of endocrine disruptors, what do we know from animal and human studies?', *Environment International* Volume: 70 Pages: 15-24 SEP 2014

7. Riffle B W, Klinefelter G R, Cooper R L et al. ', *Reproductive Toxicology*, Aug 2014, Vol 47, Pp 59-69

8. Qian L, Xiaoqian G, Yamei C et al, 'Cellular Mechanism of the Nonmonotonic Dose Response of Bisphenol A in Rat Cardiac Myocytes', *Environmental Health Perspectives*, 2014, Vol 122, Issue 6, Pp 601-608

9. Fong P P, Ford A T, 'The biological effects of antidepressants on the molluscs and crustaceans: A review', *Aquatic Toxicology*, 2014, Vol 151, Special Issue, Pp 4-13

10. Vandenberg L N, 'Non-monotonic dose responses in studies of endocrine disrupting chemicals: bisphenol a as a case study', *Dose-Response*, 2014, Vol 12 Issue 2, Pp: 259-276

11. Hu J, Juan L, Jianshe W et al, 'Synergistic effects of perfluoroalkyl acids mixtures with J-shaped concentration-responses on viability of a human liver cell line', *Chemosphere*, Vol 96, Feb 2014, Pp 81-88

12. Mater N, Geret F, Castillo L, et al 'In vitro tests aiding ecological risk assessment of ciprofloxacin, tamoxifen and cyclophosphamide in range of concentrations released in hospital wastewater and surface water', *Environment International*, Vol 63, Feb 2014, Pp 191-200

13. Khalil N, Ebert J R, Wang L et al, 'Bisphenol A and cardiometabolic risk factors in obese children', *Science of The Total Environment*, Vol 470, Feb 2014, Pp 726-732

14. Kim J H, Sartor M A, Rozek L S et al, 'Perinatal bisphenol A exposure promotes dose-dependent alterations of the mouse methylome', *BMC Genomics*, Vol 15, Jan 2014, Article Number: 30

15. Vandenberg L N, Colborn T, Hayes T B et al, 'Regulatory decisions on endocrine disrupting chemicals should be based on the principles of endocrinology', *Reproductive Toxicology*, Vol 38, 2013, Pp 1-15

16. Qinqin L, Mi T, Zhanfen Q et al, 'Research Progress in Non-Monotonic Dose-Response of Endocrine Disruptors', *Asian Journal of Ecotoxicology* , Vol 8 Issue 3, Junhe 2013, Pp 295-305

17. Gao Q, Zhu T, Guo F et al, 'Nonylphenol, an environmental estrogen, affects voltage-gated K+ currents and L-type Ca2+ currents in a non-monotonic manner in GH(3) pituitary cells',
18. *Toxicology Letters*, Vol 218 Issue 2, April 2013, Pp 137-143

19. Makwana O, Ahles L, Lencinas A et al, 'Low-Dose Trichloroethylene Alters Cytochrome P450-2C Subfamily Expression in the Developing Chick Heart', *Cardiovascular Toxicology*, Vol 13 Issue 1, 2013, Pp 77-84

20. Toshihiro E, Masaki K, Yukari U et al, 'Executive Function Deficits and Social-Behavioral Abnormality in Mice Exposed to a Low Dose of Dioxin In Utero and via Lactation', *PLOS One*, Dec 2012, Vol 7 Issue 12, Article Number: e50741

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