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Dear Commissioner Dalli; Dear Dr. Garkov:

We welcome the new guidance of the Commission's Scientific Committee on Emerging New Health Risks (SCENIHR), on how to perform risk assessments (RA).[1] We hope it represents the view of all three of the Commission's non-food safety advisory bodies (SCENIHR, SCHER, SCCP). However, the guidance contains a flaw that is likely to undermine its intent.

The guidance is a positive step towards making risk assessment as practised realistic, by minimizing false negative error - i.e. missing toxic effects. Specifically, we commend the SCENIHR for guiding its RA Working Groups to:

1) perform a thorough review of the peer-reviewed literature at the start of every RA, then consider the totality of the data using a 'weight of the evidence' approach;

2) rely "primarily on original refereed [peer-reviewed] publications" for RAs.

[1] SCENIHR (2012). Memorandum on the use of scientific literature for human health risk assessment purposes - weighing of evidence and expression of uncertainty
http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_s_001.pdf

Point (2) is critical. The peer-reviewed toxicity studies that are largely publicly funded and use flexible, realistic protocols are, according to scientific reviews, far less likely to produce false negative error than the toxicity studies sponsored by the substance's manufacturer, which follow rigid and limited OECD protocols.[2] We commend the SCENIHR for recommending that the independent peer-reviewed literature (as opposed to studies commissioned by industry, which generally are not peer-reviewed or published) should be regularly utilized in RA.

However, we are **very concerned to see this more scientifically-rigorous approach undermined, once again, by the "Klimisch loophole**". In SCENIHR's discussion of criteria for the acceptability of a study for a RA, the guidance recommends that the Working Groups utilize:

> "the criteria proposed by Klimisch et al., (2007) and the OECD Manual for the investigation of HPV chemicals."

This is unacceptable. Klimisch and co-authors were employees of the chemical giant BASF and they published in a journal that was the subject of a US Congressional inquiry due to its industry sponsorship and perceived lack of independence on chemicals.[3] Klimisch et al allow only one criterion for the most reliable studies: *Was it done according to Good Laboratory Practice (GLP)*?[4]

This criterion effectively excludes most independent (non-industry sponsored) studies from consideration, since only industry studies are done according to GLP. GLP is not a hallmark of good or reliable science: it is a laboratory management system invented for the purpose of preventing fraud in industry studies conducted for regulatory purposes. Researchers operating independently of industry consider GLP to be irrelevant to their research – and thus too expensive in terms of labour hours to implement without good reason. Crucially, at no point have regulators informed independent scientists that their study is considered unreliable for not using GLP.

We ask the Commission to immediately delete the "Klimisch loophole" from all RA guidance (EFSA, EChA and possibly other Commission guidances also use the Klimisch loophole to exclude independent peer-reviewed data). *Risk assessors must not be allowed to dismiss the valid studies they have just been asked to prioritize.*

SCENIHR's reference to the Organisation for Economic Co-operation and Development (OECD) HPV Manual compounds the Klimisch loophole. As with GLP, OECD's toxicity test protocols are for studies done for regulatory purposes (usually by industry). An increasing number of scientists operating independent of industry feel the narrow OECD protocols restrict their freedom to investigate; criticizing them as insensitive and prone to false negative results.[5] For example,

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[2] Bekelman JE, Li Y, Gross CP. Scope and impact of financial conflicts of interest in biomedical research. JAMA 2003;289:454e65.
– Fagin D, Lavelle M. Center for Public Integrity. Toxic Deception: How the Chemical Industry Manipulates Science, Bends the Law and Endangers Your Health. 2nd Edition. Monroe, ME: Common Courage Press, 1999:
– Swaen GM, Meijers JM. Influence of design characteristics on the outcome of retrospective cohort studies. Br J Ind Med 1988;45:624e9.
– vom Saal FS, Hughes C. An extensive new literature concerning low-dose effects of bisphenol A shows the need for a new risk assessment. Environ Health Perspect 2005;113:926-

[3] RTP was one of several industry-linked organizations that were investigated by a US Congressional Committee in 2008 over their role in the FDA's decision allowing the chemical bisphenol A in infant formula and other foods. See: Layton, L. 2008. Studies on chemical in plastics questioned. Washington Post. April 27, 2008. http://www.washingtonpost. com/wp-dyn/content/article/2008/04/26/AR2008042602126. html?sid=ST2008042602242 ; Dingell, Rep. J. D. (D-Mich.). 2008. Letter to Jack N. Gerard, president and CEO, American Chemistry Council, April 2. http://www.ewg.org/release/congress-chemical-industry-you-re-under-investigation

[4] Klimisch, H. J., M. Andreae, et al. (1997). A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data. Regul Toxicol Pharmacol 25(1): 1-5.

[5] Makris SL 2011. Current Assessment of the Effects of Environmental Chemicals on the Mammary Gland in Guideline Rodent Studies by the U.S. Environmental Protection Agency (U.S. EPA), Organisation for Economic Co-operation and Development (OECD), and National Toxicology Program (NTP). Environ Health Perspect 119:1047-52. http://dx.doi.org/10.1289/ehp.1002676

OECD protocols kill the test animals before most chronic disease can show up, and Ramazzini Institute's chronic toxicity tests prove this greatly understates the carcinogenicity of chemicals.

Altogether, not one of several hundred experienced risk assessors asked in plenary at the 2009 Global RA Forum could recall a single pre-marketing RA that did *not* use an OECD/GLP study as its key study to set the "safe" dose for human exposure. In post-market RA, this is not much better. For example, EFSA, in their most recent post-marketing RA of bisphenol A (BPA) appear to have used OECD/GLP compliance as the criterion to dismiss without further justification 216 of 229 (94%) of recently published studies, of which a substantial number seriously challenged or contradicted EFSA's "safe" daily dose of BPA.[6]

While the OECD protocols and GLP rules have useful elements, and GLP must continue to be used for industry studies as a tool to assist fraud detection; industry studies using these protocols must not be given greater weight than financially disinterested studies using realistic protocols.

If you wish to test whether RAs yield as much false negative error as we claim, we propose that you perform comparative literature reviews on the chronic toxicity findings for several long-marketed agents (so that they have a large enough body of peer-reviewed studies), comparing the findings of GLP/OECD regulatory studies with those of the independent literature. RA theory requires that there be a valid reason not to use the lowest chronic L/NOAEL known as the key study. We are asking you to test if RA is currently doing so.

We are confident that you will discover, for any such chemical, falsifications of OECD/GLP findings in mammalian chronic toxicity models; as well as massive data gaps hinted at by independent low-dose *in vitro* and ecotoxicity findings.

EU laws already allow the Commission to designate alternative data quality criteria as equally valid to the OECD's. So we ask the Commission to designate: 1) peer-reviewed publication, 2) high journal impact factor, and 3) researcher financial independence, as those criteria.

EFSA's June scientific colloquium on low-dose toxicity in RA would be a good forum for the EU's safety regulators to initiate this discussion on improving RA. Speakers will include Laura Vandenberg, whose review[7] found 840 published studies in which low concentrations were demonstrated to be more potent than higher ones. Such findings are routine in endocrinology; and their existence falsifies the fundamental tenet of RA, that "the dose makes the poison" in linear dose-response fashion.

In conclusion, we ask you to delete the Klimisch loophole from SCENIHR's and other guidances; and to initiate discussions with us and financially un-conflicted scientists on how to make RA more realistic. The director of the USA's National Toxicology Program and National Institute for Environmental Health Sciences has just called for such a discussion;[8] and several medical societies have offered their expertise in the effects of contaminants on human disease to assist risk assessors.[9]

We look forward to your response,

– vom Saal FS, Myers JP 2010. Good Laboratory Practices Are Not Synonymous with Good Scientific Practices, Accurate Reporting, or Valid Data. Environ Health Perspect 118:a60-a60. http://dx.doi.org/10.1289/ehp.0901495

[6] http://reseau-environnement-sante.fr/2012/05/03/ressources/veille-scientifique/bisphenol-a-bulletin-de-veille-scientifique-n-12/

[7] Vandenberg LN, Colborn T, Hayes TB, Heindel JJ, Jacobs DR Jr, Lee DH, Shioda T, Soto AM, Vom Saal FS, Welshons WV, Zoeller RT, Myers JP. Hormones and Endocrine-Disrupting Chemicals: Low-Dose Effects and Nonmonotonic Dose Responses. Endocr Rev. 2012 Mar 14 ahead of print.

[8] http://ehp03.niehs.nih.gov/article/fetchArticle.action?articleURI=info%3Adoi%2F10.1289%2Fehp.1205179

[9] http://www.sciencemag.org/content/331/6021/1136.1.citation

Yours sincerely,

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