Gezondheidsraad
Health Council of the Netherlands

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Date:	June 27, 2018	Your ref:	e-mail dated March 8, 2018	E-mail:	pw.van.vliet@gr.nl
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Subject: Comments on draft report Phenytoin

Dear Dr. Lentz,

Thank you for accepting the invitation to comment on the draft report Phenytoin, that the Health Council published for public review in December 2017.

The Council's Subcommittee on the Classification of Substances Toxic to Reproduction is pleased that NIOSH supports the outline of the report and the recommended classification and labelling. The extensive suggestions made by Drs. Olgun and Rocheleau to improve the report have been very helpful.

They noted that some recent human studies of adverse effects on fertility or offspring development were lacking. Some of the references proposed for inclusion are reviews or meta-analyses, however. The Committee bases classification and labelling of substances for reproductive toxicity on primary publications. Therefore, the reviews were used as a source of extra references only. The meta-analyses have been included in the report, because they represent additional analyses of the data. In addition, several primary studies mentioned have been included (some as 'consulted but not cited'). Together, the results of the studies added strengthen the human evidence and underpin the conclusions. The Committee did not include any references from the review by Fan and colleagues, because it focuses on effects of exposure to phenytoin in adults. The Committee also excluded the papers describing changes in sex hormone levels without changes in any other reproduction-related endpoints. These papers were excluded, because the relationships between these changes and fertility are not sufficiently clear for the hormonal changes to be used in classification. This explanation has been added in Chapter 1.
Regarding the animal studies, the Committee has kept the sentences about missing information on maternal toxicity. Results of maternal toxicity analysis are crucial to correct interpretation of teratogenicity findings (cf. EU regulation 1272/2008 and the additional considerations described in Annex E (moved to Chapter 1 in the final version)). As suggested, maternal toxicity is described first, offspring toxicity next.
Furthermore, NIOSH's remarks led to a variety of improvements throughout the report. Please bear in mind that some of the wording has been left unchanged, because it has been taken from the EU regulation.

The accompanying e-mail contains a link to the final report on Phenytoin.

Yours sincerely,

P.W. van Vliet, Ph.D.
Scientific Secretary

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