March 7, 2018

Health Council of the Netherlands
Attn: P.W. van Vliet, Ph.D.
PO Box 16052
2500 BB, The Hague
the Netherlands

Dear Dr. van Vliet:

Thank you for the opportunity to review the draft report on *Phenytoin* prepared by the Subcommittee on the Classification of Reproduction Toxic Substances, a committee of the Dutch Expert Committee on Occupational Safety (DECOS). Comments are enclosed that were prepared by Nicole Olgun, Biologist, NIOSH/HELD, 1095 Willowdale Road, Morgantown, WV 26505 and Carissa Rocheleau, Epidemiologist, NIOSH/Division of Surveillance, Hazard Evaluations, and Field Studies, 1090 Tusculum Avenue, Cincinnati, OH 45226.

If you have any questions regarding the comments, please contact me at 513-533-8260 (telephone) or by Email at tbl7@cdc.gov.

Sincerely yours,

Thomas J. Lentz, Ph.D., M.P.H.
Branch Chief
Document Development Branch
Education and Information Division

1 Enclosure

Comments on DECOS draft document on Phenytoin **By: Nicole S. Olgun, Biologist, NIOSH/Health Effects Laboratory Division, 1095 Willowdale Road, Morgantown, WV 26505** **and Carissa Rocheleau, Ph.D., Epidemiologist, NIOSH/Division of Surveillance, Hazard Evaluations, and Field Studies,** **1090 Tusculum Avenue, Cincinnati, OH 45226**

SECTION & PARAGRAPH	COMMENT

General Comments	This document reviews the reproductive toxicity of phenytoin in humans and various animal models. Although it is clear that a thorough literature review was conducted, several, more recent references should be included, to help strengthen this evaluation (they are mentioned below). Phenytoin is an anti-epileptic drug, administered either as a monotherapy, or as part of a combined therapy. The authors make it clear that the focus is on the effects of phenytoin as a reproductive toxicant. What is not clear, is how phenytoin would be an occupational exposure. Page 5, lines 10-14 mention that occupational exposure to phenytoin can occur in pharmacies or industry settings. There is a reference to occupational exposures at the end of the document (Page 43, Line 27 and Page 45, Line 6), but nothing relevant in the reviewed studies. Therefore, the link between occupational exposure to phenytoin and adverse reproductive outcomes is unclear. Several important human studies are not reviewed or consulted which may affect the conclusion around human studies. I have provided citations for 5 manuscripts that should have been identified given the described search terms and dates, contain relevant data on phenytoin monotherapy, were generally well-conducted, had a relatively large sample size, and were published in respected mainstream journals. The omission of these articles raises concerns about the adequacy of the literature search and screening; there may be additional relevant articles of which I am unaware. The inclusion of these omitted studies may somewhat strengthen the human evidence of developmental toxicity. The summary of the evidence for developmental effects in humans (pages 42-43) should be evaluated and revised in light of this additional evidence. Also, the section describing animal studies would benefit from a description of animal doses that approximate human therapeutic ranges. In rodents, high mortality can be observed with phenytoin at doses that are not outside of human clinical parameters. This is one of the major limitations of rodent studies in this model. Also, most of the relevant and appropriate references date back to the 1980s or 1990s, and are used for recommendations in 2018.

	Based on the definition given on page 65, Fertility could potentially be classified as Category 2. The male fertility studies mentioned in the beginning of this document show evidence of decreased sperm motility after liquefaction (Chen 1992), decreased sexual interest and function levels, as well as lower serum dehydroepiandrosterone sulfate, etc.(Herzog 2006) and decreased animal fertility rates. Please see the comments below on studies to include for female fertility. This might strengthen the decision to use Category 2. The recommendation for developmental toxicity falling under category 1B seems appropriate. "Lactation" has its own hazard category (bottom of page 65). Based on the information provided in this document, studies on lactation were divided into two categories: the concentration of phenytoin in breast milk, and the effect on the IQs of children that ingested breast milk from phenytoin-exposed mothers. The authors make it clear that the IQs did not differ in breast fed versus non-breast fed (page 24, Meador et al, 2010; Meador et al, 2014). However, in the other phenytoin concentration studies described in this section, numbers are reported, but they do not always tell the reader the significance of the numbers. Therefore, it is difficult to assess whether the decision to "not categorize" lactation is appropriate. However, a summary on lactation is provided on pages 44-45. Based on page 45, lines 3-5, lactation might fall under category (c) (page 66): "absorption, metabolism, distribution and excretion studies that indicate the likelihood that the substance is present in potentially toxic levels in breast milk." The key word is "potentially." The inclusion of the Regulation (EC) 1272/2008 of the European Community, Section 3.7 "Reproductive toxicity" is very helpful (pages 63-78).

Add reviews of key human studies	Statistics for phenytoin treatment at weeks 5-12 from last menstrual period, stratified by folic acid during those same weeks, are summarized in table 3 of this reference: Kjaer D, et al. [2008]. Antiepileptic drug use, folic acid supplementation, and congenital abnormalities: a population-based case-control study. BJOG 115(1):98-103. Statistics for monotherapy with phenytoin are provided in table 4 of this reference: Holmes LB, et al. [2001]. The teratogenicity of anticonvulsant drugs. N Engl J Med12:344(15):1132-1138. Statistics for monotherapy for phenytoin are provided in tables 2, 4, 5, and throughout the text, for both minor and major malformations as well as neurodevelopmental outcomes: Dean JC, et al. [2002]. Long term health and neurodevelopment in children exposed to antiepileptic drugs before birth. J Med Genet 39(4):251-259. Statistics for specific major congenital malformations by type of AED therapy, including results for phenytoin monotherapy, are presented in table 4: Werler MM, et al. [2011]. Use of Antiepileptic Medications in Pregnancy in Relation to Risks of Birth Defects. Annals of Epid 21(11):842-850. Statistics for major congenital malformations, and by type of malformation, are provided for phenytoin monotherapy in tables 2 and 3: Morrow J, et al. [2005]. Malformation risks of antiepileptic drugs in pregnancy: a prospective study from the UK Epilepsy and Pregnancy Register. J Neurology, Neurosurgery, Psychiatry 12:77(2):193-198.

	Be consistent and use the word "offspring" throughout the document, as opposed to "progeny." Sometimes numbers are spelled out, example "nine" and other times they are written..."9" - Should be consistent. Throughout this document, many other review articles and experiments conducted by other authors are cited. Often, the author being cited is mentioned in the first or second sentence of the paragraph, but not consistently. It might be easier for the reader, and more uniform, if the "author, year" are listed first, before the review of their study begins. Example: (as seen on page 28) Rats **Rowland et al. 1990** Text about Rowland's study **Zengel et al. 1989** Text about Zengel's study
	The critical studies summarized in this review, in reference to phenytoin toxicity, list all of the important outcomes, but sometimes, in order to understand whether or not phenytoin toxicity existed, the section had to be re-read several times. Perhaps at the end of every section, a paragraph or bullet points that summarize the most important findings would be helpful to the reader.
	Throughout the document, *P*-values are listed, but there is no mention of what the significance is being compared to. It would be assumed to be to "control" groups, but it should always be clarified. Please see page 29, lines 16 and 18 and other places in the document.

	If Appendix F were to be redone (see specific comments below), the animal section, which starts on page 26, could be significantly revised. The review of the studies should follow some sort of uniform format, so the reader will know where to find the desired information in every study. Perhaps the authors could omit sentences about toxicities that were not reported, so the reviews are more concise. For example "no information on maternal toxicity was reported" is mentioned several times. This sentence can be omitted. Alternately, keep all the species together, and then subdivide them according to method of drug administration. Example: **Mice** **a. Fertility** **b. Structural Defects According to Method of Drug Administration** **B1. Gavage** **Author 1** **Summary Text 1** **Author 2** **Summary Text 2** **B2. Water Intake** **Author 1** **Summary Text 1** **Author 2** **Text 2** **B3. Gastric Intubation** **Rats** **a. Fertility** **b. Structural Defects According to Method of Drug Administration** **B1. Gavage** **B2. Water Intake**
	Sometimes, in the animal studies section, the authors write about offspring toxicity, then maternal toxicity, and then something else about the offspring. It would be easier to read if all of the maternal or paternal toxicities were addressed first, and then the offspring toxicities.
Specific Comments	

Page 5, Line 3	Should read "the effects of phenytoin on reproduction" instead.
Page 5, Line 13	Suggest using the word "workers" instead of "man". Seems more inclusive of men and women this way.
Page 5, Line 26-End of Page 6	Does "effects on development" mean offspring development throughout gestation, or only during a certain period of exposure during gestation? Does the lack of sufficient data to classify phenytoin apply to both male and female fertility? This should be specified. The term "effects on or via lactation" is not clear. It is unclear as currently stated, whether breastmilk quality/quantity is affected, or if this refers to the detection of certain components in the breastmilk, or if the overall process of "lactation" is impacted.
Page 7, Line 27	"as well as lactation of…." Not sure what this means. Is this referring to the effect of phenytoin on endogenous compounds found in breastmilk? The term "lactation" by itself is referring to the secretion of milk from the mammary gland, so it is unclear if the process of milk secretion is being affected, or what is being excreted into the milk.
Pages 7-8, Classification Table	It is confusing to read "reproduction (Fertility (F))." Perhaps rename it to something Like "Classification as related to Fertility (F) and Development (D)". It is already understood that this entire document is related to reproduction. It would also be beneficial to be as specific as possible. "No classification" should be re-worded. The authors are using the Regulation (EC) 1272/2008 of the European Community for section 3.7, reproductive toxicity. It would read better if the authors stated something like "X does not meet the requirements to be classified as a reproductive toxicant as defined by regulation 1272/2008 of the European Community…" "Fertility" should be specified: male, female, or both. "Development" would read better as "offspring development." Again, the term "effects on or via lactation" needs to be clarified. Is what you mean "harm to breast fed children" as stated in H362?
Page 8, Hazard Statement Codes	Sometimes "d" and "f" are capitalized. Is this significant?
	"unborn child" can also be written as "developing fetus."

Page 9, Lines 5-7	It states that the committee is considering the concentration of a compound as potentially toxic to breast fed children according to acceptable daily intakes (ADIs) for the general public. Do infants/children have different ADI guidelines for the specified compounds as compared to adults?
Page 9, Line 11	Does this mean that the last search was performed in July 2017, or the latest content included was up until July 2017?
Page 9, Line 21	Should read "In the assessment of the potential adverse effects of phenytoin on reproduction…"
Page 12, Line 3	Do you mean to say that "women that suffer with epilepsy are at an increased risk for adverse reproductive outcomes?" Or, are you referring to a dysfunction of the placenta or uterus that does not necessarily impact reproductive outcomes?
Page 12, Lines 8-10	Is this supposed to say that since pregnant women suffering from epilepsy are often given a combination of antiepileptics, that the evaluation of phenytoin on reproductive outcomes is more difficult? What exactly is being evaluated?
Page 13, Lines 1-2	Does "high similarity" mean the same thing as there was no statistical significance detected between the groups? Also, perhaps mention the significance of testosterone, LH, and FSH, so the reader will know what changes in these concentrations signify or why they are important. Also, define the abbreviations LH and FSH.
Page 13, Lines 2-4	Are the lower seminal volumes and spermatozoa concentrations lower when compared to controls? It is confusing as written. Are the *P*-values referencing significance when compared to the controls, or when the two groups are compared to one another?
Page 13, Line 13	*In vivo* usually refers to animal studies, not human studies.
Page 14, Lines 7-8	Something needs to be mentioned here, even if it is only one study or a brief review of what is currently known. It is apparent that this is an area that is lacking in knowledge now, but having *some* information strengthens this document. Suggestions: Isojärvi JI, Taubøll E, Herzog AG [2005]. Effect of antiepileptic drugs on reproductive endocrine function in individuals with epilepsy. CNS Drugs 19(3):207-223. Bauer J, Cooper-Mahkorn D [2008]. Reproductive dysfunction in women with epilepsy: menstrual cycle abnormalities, fertility, and polycystic ovary syndrome. Int Rev Neurobiol 83:135-155.

Page 14, Line 10	Though the two surveillance studies included for structural defects are relevant, perhaps include the following two as well, as they are both more recent, and also describe structural defects as a result of maternal phenytoin exposure. Veroniki AA, Cogo E, Rios P, Straus SE, Finkelstein Y, Kealey R, Reynen E, Soobiah C, Thavorn K, Hutton B, Hemmelgarn BR, Yazdi F, D'Souza J, MacDonald H, Tricco AC [2017]. Comparative safety of antiepileptic drugs during pregnancy: a systemic review and network meta-analysis of congenital malformations and prenatal outcomes. BMC Med 15:95 Weston J, Bromley R, Jackson CF, Adab N, Clayton-Smith J, Greenhalgh J, Hounsome J, McKay AJ, Tudur Smith C, Marson AG 2016]. Monotherapy treatment of epilepsy in pregnancy: congenital malformation outcomes in the child. Cochrane Database Syst Rev 11:CD010224.
Page 15, Line 11	If the authors of the 2012 Vajda et al. manuscript did not explicitly mention that the exclusion criteria were those of EURAP, it should not be mentioned in the review, even as an assumption.
Page 15, Lines 21-23	It is stated that at three months of age, none of the children showed cardiac malformations. However, line 21 states that the children were followed up until age 6. Did anything happen between 3 months and 6 years of age?
Page 16, Line 1	"in utero" should be in italics throughout the document
Page 16, Line 2	"offspring unexposed" does not make sense. Perhaps say "in cases where the children were not exposed to epileptic drugs *in utero*…." Alternately, wouldn't these be the controls since they were not exposed to antiepileptics?
Page 18, Line 16	Thus far, the study summaries have started with the most recent year and worked backwards. This section, titled "Follow-up studies of vigilance centre data" starts with the oldest study, and then moves toward the more recent ones. The document's format should be consistent.
Page 19, Line 34	"…were either incompletely or not reported…"
Page 21, Line 1	A more recent study on growth is available: Fan HC, et al. [2016]. The Impact of Anti-Epileptic Drugs on Growth and Brain Metabolism. Int J Mol Sci 17:1242.
Page 22, Line 36	This study summary would be more appropriately placed under "Growth" (Page 21, Line 1).

Page 24, Line 24	The term "lactation" might lead the reader to believe that the studies reviewed will be in reference to whether or not phenytoin or its metabolite(s) passes through the breast milk, or affects the ability of the mother to lactate. Instead, the Meador et al. study investigates the effect of breastfeeding on IQ. Consider using this under a different category name, since IQ is more "cognitive." Starting with the Shimoyama study in 1998, is where the term "lactation" seems appropriate. If you wish to include cognitive issues during breastfeeding, more recent publications are available: Veroniki AA et al. [2017]. Comparative safety of antiepileptic drugs for neurological development in children exposed during pregnancy and breast feeding: a systematic review and network meta-analysis. BMJ Open. 2017; 7:e017248. A more recent study more directly related to phenytoin concentrations in breast milk: Harden CL et al. [2009]. Management issues for women with epilepsy—focus on pregnancy (an evidence based review): III. Vitamin K, folic acid, blood levels, and breast feeding. Epilepsia 50(5);1247-1255.
Page 26, Line 16	"5/group" should read "n=5 per group."
Page 26, Line 25	How old were the mice "2 days prior to necropsy?"
Page 26, Lines 28-31	This part is confusing. Fertility was measured by placing a male with two females in a cage for 5 days. What does "phenytoin 5/10 and control 7/11 mean?" Does it refer to the number of females that became pregnant? How is the denominator 11, if there were 2 females/cage? 11 is not divisible by 2. Please clarify this study.
Page 26, Line 32	Should read "n=5-7 per group."
Page 27, Line 3	Units needed for testis, epididymis, and coagulating gland.
Page 28, Line 1	It is not necessary to list the method of administration since it is mentioned in every individual study (gavage).
Page 28, Line 3	Should be "were administered phenytoin daily…"
Page 28, Lines 10-11	Maternal deaths are mentioned, however, it also says 2/8 dams and 3/4 dams. Please clarify. Is this in reference to how many pups were non-viable?
Page 28, Lines 15-16	Instead of including $p < 0.05$ for all, it would be easier to read "significant decreases in fetal weight, crown rump length and reduced ossification… "
Page 28, Lines 27-29	Please provide number of females in each treatment group for the Zengel et al. study (1989).

Page 28, Line 31	Please note the composition of the 135 pups sacrificed for analysis in Zengel et al. (1989) study—how many came from each treatment group?
Page 28, Line 34	It is not necessary to include the number of pups that were still alive. Perhaps state that "At the time of weaning at PND 25, all viable pups…" Likewise, the following line should say non-viable, as opposed to "dead."
Page 28, Line 39	The time points should be specified. Line 38 is confusing because the statistics for treated females are mentioned and then it says that males were more affected than females.
Page 29, Lines 1-4	Instead of listing all *P*–values separately, and then listing the changes in craniofacial morphology, it would be easier to understand if the craniofacial morphologies were listed, with the individual *P*-value for that morphology in parentheses afterwards. Example: small head ($P < 0.005$), hypertelorism ($P < 0.01$).
Page 29, Line 5	"at levels" should be "doses."
Page 29, Lines 5-7	Please provide the number of dams per treatment group for the Lorente et al (1981) study.
Page 29, Lines 9-12	It is stated that the dose of 1,000 mg/kg bw/d was chosen because of the low rates of maternal mortality. The next sentence then states that information on maternal mortality was not reported. This is contradictory.
Page 29, Line 22	When animals are treated, they are dosed. "at levels" is not the proper term.

Page 30, Lines 2-9	This summary is confusing. It seems to highlight the lack of significance detected, lack of information for time point and dosing of lesions, and lack of maternal toxicity. It does not make a very strong case for either the presence or lack of phenytoin toxicity and should not be included. More recent studies are available and should be included: Mao XY, et al. [2010]. Effects of phenytoin on Satb2 and Hoxa2 gene expression in mouse embryonic craniofacial tissue. Biochem Cell Biol 88(4):731-735. Even though the above reference investigated gene expression, it is more current than a study from 1984, and mentions the effects of phenytoin on cleft palate gene expression in mouse embryos. It might also be worthwhile to include the following study : Danielsson BR et al. [2005]. Phenytoin teratogenicity: hypoxia marker and effects on embryonic heart rhythm suggest an hERG-related mechanism. Birth Defects Res A Clin Mol Teratol 73(3):146-153. Even though this does not talk about a "structural defect", it is important to include recent studies using modern techniques, as opposed to studies dating as far back as the 1970s. It does not make sense to make and/or suggest recommendations for the safety of a drug, when the recommendations are based on very old studies.
Page 30, Line 24	The method of drug administration here is gastric intubation, but it is under the "gavage" heading, so it is inappropriately placed.
Page 30, Line 32	The lack of pregnant females at 105 mg/kg in the study by Roberts et al. (1991) is perhaps worth noting in the section on female fertility studies, too.
Page 31, Line 22	Perhaps use "Water Intake" instead.
Page 31, Lines 29-31	The sentence does not make sense.
Page 32, Lines 12-13	It does not matter if the data are not shown for the purpose of experimental review. The reviews presented in this document should be as streamlined as possible.
Page 32, Line 32	Again, if a certain toxicity was not reported, there is no need to mention it in the review. List only the most important information.
Page 33, Line 10	Use the word "dose", not "level."
Page 34, Line 26	Lack of something being reported does not need to be included.

Page 37, Lines 5-6	Suggest re-writing the sentence to read: "Compared to controls, pup death in the high-dose group was not statistically significant."
Page 38, Lines 11-41	Please provide the number of rats per treatment group in each of the three experiments for the Vorhees (1983) study.
Page 39, Lines 12-17	This short paragraph does a wonderful job of letting the reader know what to expect. Because of the large number of studies reviewed, it would be helpful to include something similar for the other categories.
Page 40, Lines 34-35	This last sentence is a good summary of the importance of the study. A summary of important points needs to be included at the end of every study or at the end of every section with a group of studies.
Page 41, Line 5	What is meant by functional fertility? How is it different from the parameters related to fertility mentioned in the next sentence?
Page 41, Lines 9-20	This discussion does not seem to belong in a "conclusion" section. This is a review of work previously done by others. Only lines 20-21 seem to belong in a conclusion section. This section should not focus on summarizing individual studies.
Page 41, Lines 22-29	This paragraph is a summary of previously conducted studies, and could belong in the animal fertility study section that begins on page 27.
Page 41, Lines 30-35	This is the only paragraph on this page that reads like a "conclusion." The wording should be more convincing. For examples, state "In conclusion, phenytoin has not been adequately assessed….." or something similar. This sentence is confusing: "…the Committee recommends not classifying phenytoin due to a lack…" Not classifying phenytoin as what? Is it saying that phenytoin is thought to not affect fertility based on available studies? See previous comments concerning classification wording.
Page 41	The fertility conclusion section should be subdivided into "human" and "rodent."
Page 42, Lines 3-10	This paragraph should preface the section on human developmental studies that begins on page 14, so the reader understands why the studies described in that section were important.

Page 43, Lines 19-21	This sentence is important, but confusing. Are the authors saying that due to a lack of sufficient human data, they CANNOT classify phenytoin as a known, human developmental toxicant? On this same page (line 16), it is suggested that phenytoin is a developmental toxicant and is often considered to be a teratogen by clinicians. The last sentence which starts on Line 19 contradicts this, citing insufficient human data. Therefore, the viewpoint of the authors is not clearly communicated.
Page 43 , Line 22	Most of this section, "Developmental effects in animals", is a review of previous work, and does not belong in the conclusion.
Page 45, Lines 13-15	The sentence states that information on the plasma levels of women occupationally exposed to phenytoin is not available. As mentioned in the beginning, under "general comments", occupational exposure of phenytoin as it relates to reproductive toxicity is not clear.
Page 79, Appendix F	Table 1 should be renamed "*In Vivo* Fertility Studies." It is understood that it pertains to phenytoin. The table could be re-arranged so the reader can easily locate the most important information. "Authors" – This is fine, but for every category, it should be consistent starting with the most recent study. Below is an example of how the table could be revised to make it easier for the reader. As is, it is too wordy. If the reader wants more details, they can either refer to the appropriate review in the document, or the original manuscript.

***In Vivo* Fertility Studies**
Male- Rats

Reference	Treatment Groups	Reproductive Toxicities	Other Toxicities
Shetty, 2007	Route of Administration- Oral gavage Controls – Phenytoin- 0, 40, 65, 105 mg/kg bw/day	Decreased fertility Decreased sperm motility Decreased reproductive organ weights (105 mg/kg only)	None reported OR Necrosis at injection site

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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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