DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Centers for Disease Control and Prevention
National Institute for Occupational
Safety and Health
1090 Tusculum Avenue
Cincinnati OH 45226-1998

September 12, 2014

The Health Council of the Netherlands
Attn: Dr. G.B. van der Voet
PO Box 16052
2500 BB The Hague
The Netherlands

Dear Dr. van der Voet:

Thank you for the opportunity to review the draft report on *Adriamycin* prepared by the Dutch Expert Committee on Occupational Safety (DECOS). Comments are enclosed that were prepared by Thomas Connor, NIOSH/DART, 1090 Tusculum Ave., Cincinnati, OH 45226-1998 and Liying Rojanasakul, NIOSH/HELD, 1095 Willowdale Rd., Morgantown, WV 26505-2888.

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

NIOSH review comments on DECOS draft Adriamycin
by Thomas Connor, NIOSH/DART, 1090 Tusculum Ave., Cincinnati, OH 45226-1998 and Liying Rojanasakul, NIOSH/HELD, 1095 Willowdale Rd., Morgantown, WV 26505-2888

SECTION & PARAGRAPH	COMMENT *See examples below.*
General Comments	Adriamycin is another name for "Doxorubicin" which is also commonly used. The provided document gives general information on Adriamycin and its toxic effects with key published in vitro/in vivo/human study data. Additional studies are cited below for consideration.
Specific Comments	
Section 2	Reference 9 contains more information than indicated "the identity and some physicochemical properties of Adriamycin are given below [4,5,7-10]" (page 7). It should be also cited at 2.2, *i.e.*, "Evidence for carcinogenicity…", " Adriamycin (Doxorubicin hydrochloride): reasonably anticipated to be a human carcinogen…". http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/f?./temp/~yTxRkW:1 A recent animal study showed that Adriamycin induces cardiac fibrosis: *Protective effect of resveratrol against doxorubicin-induced cardiac toxicity and fibrosis in male experimental rats*. Arafa MH, Mohammad NS, Atteia HH, Abd-Elaziz HR. J Physiol Biochem 2014 Jun 18. [Epub ahead of print]. http://link.springer.com/article/10.1007%2Fs13105-014-0339-y [ABSTRACT ONLY]. The inclusion of some occupational exposure studies should be included even though no regulatory exposure limit is available. *Occupational exposure to carcinogens in the European Union*. Timo Kauppinen, Jouni Toikkanen, David Pedersen, Randy Young,Wolfgang Ahrens, Paolo Boffetta, Johnni Hansen, Hans Kromhout, Jeronimo Maqueda Blasco, Dario Mirabelli, Victoria de la Orden-Rivera, Brian Pannett, Nils Plato, Anja Savela, Raymond Vincent, Manolis Kogevinas Occup Environ Med 2000;57:10–18 http://oem.bmj.com/content/57/1/10.long

Section 2 (con't)	*Biological monitoring of nurses exposed to doxorubicin and epirubicin by a validated liquid chromatography/fluorescence detection method.* Pieri M, Castiglia L, Basilicata P, Sannolo N, Acampora A, Miraglia N. Ann. Occup. Hyg, 54(4):368-76 (2010) http://annhyg.oxfordjournals.org/content/54/4/368
Section 2.3	An additional article on the mutagenicity of Adriamycin was located: Matney, T.S., T.V. Nguyen, T.H. Connor, W.J. Dana and J.C. Theiss. *Genotoxic classification of anticancer drugs*. Teratogenesis, Carcinogenesis, and Mutagenesis 5:319-328, (1985)
Section 2.5	Could not locate any reference to an OEL.
Section 3	**Carcinogenicity studies** - the following references should be considered: **Doxorubicin and metastasis:** *Chemotherapy-enhanced inflammation may lead to the failure of therapy and metastasis*. Dinesh Vyas, Gieric Laput, Arpitak K Vyas. OncoTargets Ther 12(7):1015-23, 2014 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4061164/ "*Doxorubicin treatment alone potentially enhanced* metastasis *to lung in the human breast cancer MDA-MB-231 orthotopic xenograft model and metastasis to bone in the 4T1 orthotopic xenograft model, ...*". *Doxorubicin in combination with a small TGFbeta inhibitor: a potential novel therapy for metastatic breast cancer in mouse models*. Bandyopadhyay A1, Wang L, Agyin J, Tang Y, Lin S, Yeh IT, De K, Sun LZ. PLoS One 2010 Apr 28;5(4):e10365 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2860989/pdf/pone.0010365.pdf
Section F	**Animal studies:** A report showed that high-dose (10 mg/kg bw) Adriamycin treatment induces tumor in SD rats while other studies provided here showed its lethal toxicity. This paper describes the difference in tumor biodistribution compared to other studies in SD rats. *Mammary tumor induction in male and female Sprague-Dawley rats by Adriamycin and Daunomycin.* Emilio Bucciarelli. *JNCI,* 66(1): January 1981. http://jnci.oxfordjournals.org/content/66/1/81.full.pdf

Section F (con't)	**Genotoxicity and Mechanism of genotoxicity:** Studies provided here are before 1984. Below reference provides relevant publications on genotoxicity of Doxorubicin after 1984. "The anthracycline antibiotic Doxorubicin (DXR), a drug that targets topoisomerase II (Top2) (Islaih et al., 2005), is one of the most effective anticancer drugs used in the clinic (Lyu et al., 2007). This drug may induce mutations by intercalating formaldehyde adducts in the DNA (Spencer et al., 2008) or by inducing the formation of oxygen free radicals (Navarro et al., 2006), single- and double-strand DNA breaks (Lyu et al., 2007) and somatic recombination (Lehmann et al., 2003, Valadares et al., 2008, de Rezende et al., 2009 and Sousa et al., 2009)". *The effect of the dibenzylbutyrolactolic lignan (-)-cubebin on doxorubicin mutagenicity and recombinogenicity in wing somatic cells of Drosophila melanogaster*. Rezende AA, Silva ML, Tavares DC, Cunha WR, Rezende KC, Bastos JK, Lehmann M, de Andrade HH, Guterres ZR, Silva LP, Spanó MA. *Food Chem Toxicol*. 2011 Jun;49(6):1235-41 http://www.sciencedirect.com/science/article/pii/S0278691511000706
Other Information	**Recent clinical trials and applied research investigate pulmonary administration and nanoassembly of Adriamycin, albeit their toxicities have not been well studied and need further investigation.** *Pulmonary administration of a doxorubicin-conjugated dendrimer enhances drug exposure to lung metastases and improves cancer therapy*. Kaminskas LM, McLeod VM, Ryan GM, Kelly BD, Haynes JM, Williamson M, Thienthong N, Owen DJ, Porter CJ. J Control Release. 2014 Jun 10;183:18-26 http://www.sciencedirect.com/science/article/pii/S0168365914001461 [ABSTRACT ONLY]

Other Information (con't)	*Phase I study of inhaled Doxorubicin for patients with metastatic tumors to the lungs*. Otterson GA, Villalona-Calero MA, Sharma S, Kris MG, Imondi A, Gerber M, White DA, Ratain MJ, Schiller JH, Sandler A, Kraut M, Mani S, Murren JR. Clin Cancer Res. 2007 Feb 15;13(4):1246-52 http://clincancerres.aacrjournals.org/content/13/4/1246.full.pdf+html *A unique squalenoylated and nonpegylated doxorubicin nanomedicine with systemic long-circulating properties and anticancer activity*. Maksimenko A, Dosio F, Mougin J, Ferrero A, Wack S, Reddy LH, Weyn AA, Lepeltier E, Bourgaux C, Stella B, Cattel L, Couvreur P. Proc Natl Acad Sci 2014;111(2):E217-26 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3896189/
Recommendations	I concur with the recommendations for a 1B category.