

# This Week's Citation Classic

Vos J G, Koeman J H, van der Maas H L, ten Noever de Brauw M C & de Vos R H. Identification and toxicological evaluation of chlorinated dibenzofuran and chlorinated naphthalene in two commercial polychlorinated biphenyls. *Food Cosmet. Toxicol.* 8:625-33, 1970.

[Inst. Veterinary Pathol. and Inst. Veterinary Pharmacol. and Toxicol., Utrecht; and Central Inst. for Nutrition and Food Res., Zeist, The Netherlands]

Significant differences in toxicity among three polychlorinated biphenyl (PCB) mixtures had been described previously. High mortality, liver damage, and edema were associated with only two of the three PCBs. Using column and gas chromatography, several compounds were identified in the diethylether fraction of these two PCBs. A chick embryo assay confirmed the high toxicity of this fraction. Mass spectrometric and microcoulometric analyses indicated the presence of tetra- and pentachlorodibenzofuran, chemicals closely related to "dioxin." [The *SCI*® indicates that this paper has been cited in more than 210 publications.]

## Searching for a Poison in a Poison

J.G. Vos  
National Institute of Public Health and  
Environmental Protection  
3720 BA Bilthoven  
The Netherlands

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Polychlorinated biphenyls (PCBs) were first identified in 1966 in wildlife samples by S. Jensen. Soon following this report, various investigations showed their widespread environmental distribution. In The Netherlands, these studies were done by the team of Jan Koeman at the Veterinary Faculty, University of Utrecht. In order to evaluate the toxicological significance of these PCB levels in wildlife specimens, animal experiments appeared necessary. As a young doctor of veterinary medicine with some training in toxicologic pathology, I became largely responsible for these experimental studies.

Careful study of the literature showed that the little work done on the toxicology of PCBs was mainly in relation to the risks of occupational exposure, showing the potent activity on human skin (so-called chloracne) and liver. In birds PCBs induced edema and liver damage. The literature study, however, showed a striking similarity of toxic effects produced by PCBs and effects produced by technical chlorinated phenols and derivatives.

Of great importance for the understanding of the etiology of chloracne and liver damage caused by technical 2,4,5-trichlorophenol is the work of German scientists reporting in the 1950s that the contaminant 2,3,7,8-tetrachloro-

dibenzo-p-dioxin ("dioxin") was responsible for these serious lesions. Furthermore the related chemical 1,2,3,7,8,9-hexachlorodibenzo-p-dioxin, which can be formed during the pyrolysis of 2,3,4,6-tetrachlorophenol, was identified in 1968 in the US as the causative factor for the chick edema disease. From these literature data, I hypothesized that technical PCBs contain a liver necrosis-, edema-, and chloracne-causing factor.

To test this hypothesis, we initially performed a comparative toxicity study in chickens with three commercial PCBs (Phenoclor DP6, Clophen A60, and Aroclor 1260) that showed a marked resemblance in their gas chromatograms and mass spectra. In this experiment, a first indication of the presence of toxic impurities was obtained by the finding that 100 percent mortality, severe edema, and liver damage occurred following exposure to Phenoclor and Clophen, but not to Aroclor.<sup>1</sup>

In the subsequent study, the subject of this *Citation Classic*, we described the identification of polychlorinated dibenzofurans (PCDFs) as highly toxic impurities in these two most toxic PCB mixtures. We now know that these chemicals can impair immune function.<sup>2</sup> Originally, we submitted this paper to *Nature* as an article of general interest but were informed that, despite the topicality of the subject, space could not be offered for the full paper. They were glad to receive a short letter to the editor highlighting one aspect of the study. Instead, we choose to submit the paper to a specialized toxicology journal. A study that confirmed and extended our data was published later in *Nature*.<sup>3</sup>

We explained the formation of PCDFs in PCBs to be caused by a chemical reaction during the distillation of crude PCB in the presence of sodium hydroxide at elevated temperatures. Currently we know that heating PCBs under various conditions can generate significant amounts of PCDFs.<sup>4</sup> Examples are the Yusho and Yu-Cheng accidents in which more than 3,000 people in Japan and Taiwan were intoxicated by the consumption of rice oil contaminated by PCBs and PCDFs. Another example is the series of fires involving PCB-filled electrical equipment releasing soot highly contaminated with PCDFs. Generation of polychlorinated dibenzofurans (and dibenzo-p-dioxins) also has been shown to occur in municipal incinerators, releasing significant amounts in the environment through the stack gases. This is a matter of increasing concern.

1. Vos J G & Koeman J H. Comparative toxicologic study with polychlorinated biphenyls in chickens with special reference to porphyria, edema formation, liver necrosis and tissue residues. *Toxicol. Appl. Pharmacol.* 17:656-68, 1970. (Cited 115 times.)
2. Vos J G & Luster M I. Immune alterations. (Kimbrough R D & Jensen A A, eds.) *Halogenated biphenyls, terphenyls, naphthalenes, dibenzodioxins and related products*. Amsterdam, The Netherlands: Elsevier, 1989. p. 295-322. (Cited 5 times.)
3. Bowes G W, Mulvihill M J, Simoneit B R T, Burlingame A L & Risebrough R W. Identification of chlorinated dibenzofurans in American polychlorinated biphenyls. *Nature* 256:305-7, 1975. (Cited 105 times.)
4. Polychlorinated dibenzo-*para*-dioxins and dibenzofurans. *Environmental health criteria 88*. Geneva, Switzerland: World Health Organization, 1989.