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An Verteiler

Ihre Zeichen und Nachricht vom	Gesch.-Z.: *Bitte bei Antwort angeben*	Telefon	Berlin
-	FB7-2501-00-147460	01888 412 3614	17.05.2001

Meeting on Non-Dioxin-like PCBs

Dear Colleagues,

In 1998, the World Health Organization (WHO) has established a TDI of 1-4 WHO-TEQ pg/kg bw for dioxins, including PCDDs, PCDDFs and 12 dioxin-like PCBs which are assessed on the basis of their AhR-mediated effects. This approach, obviously, does not consider other PCB congeners. Non-dioxin-like PCBs are of relevance, in particular since they also accumulate in the food chain and human tissues. Therefore it seems appropriate to discuss and consider potential approaches how to deal with the overall toxicological properties of PCBs, which are not confined to AhR-mediated effects. A concept for the evaluation of non-dioxin-like PCBs is nescessary to provide guidance for managing risks emanating from exposure to this group of chemicals.

On behalf of WHO, the Bundesinstitut für gesundheitlichen Verbraucherschutz und Veterinärmedizin (BgVV) in Berlin is organizing a two day meeting to discuss concepts and approaches for the evaluation of non-dioxin-like PCBs. Once a common approach is agreed upon, follow-up work will be initiated by WHO with the aim of developing guidance on exposure to non-dioxin-like PCBs.

We appreciate your kind agreement to participate in this important endeavour, and would like to cordially invite you to participate in the meeting as an expert.

The meeting will start on **Monday, 3 September, 10.oo a.m.** and close on Tuesday, 4 September, late afternoon. It will take place at the

Bundesinstitut für gesundheitlichen Verbraucherschutz und Veterinärmedizin
(Federal Institute for Health Protection of Consumers and Veterinary Medicine)
D-14195 Berlin, Thielallee 88-92
Building 8, Large Meetingroom, 2nd Floor

A discussion paper will be prepared in advance. Participants who would like to prepare additional background papers are encouraged to do so. All documents will be circulated before the meeting. The meeting will be supported by the German Ministry for the Environment, Nature Conservation and Nuclear Safety. BgVV will act as a host and will cover your travel expenses which will be refunded according to the current legal provisions on official travel. In our previous note we have

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Naumburger Straße 96 a
D – 07743 Jena
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proposed that we will arrange all hotel reservations. To be able to do this, please let us know as soon as possible the dates of your arrival and departure.
We look forward to seeing you in Berlin.

With kind regards
Yours sincerely

Dr. W. Lingk
Dir. and Prof.

Meeting on Non-Dioxin-like PCBs

3./4.09.2001 BgVV Berlin

(当日配布された
改訂版)

List of Participants - experts and guests

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討論の骨子(案)　　当日、冒頭に提示された

RISK ASSESSMENT OF NON-DIOXIN LIKE PCBs

1. TERMINOLOGY

   * total PCBs, Aroclor equivalents, indicator congeners
   * include all ortho-substituted PCBs, only $\geq$ 2 orthos

2. EXPOSURE

   * analytical methodology
   * environmental mixtures ("weathered" PCBs) vs. commercial PCBs
   * external dose (food, etc.) vs. internal measure (body burdens)

3. TOXICOLOGY

   * commercial PCBs as surrogates?
   * individual congeners (indicators), synthetic mixtures (+/- dioxin-like PCBs?), metabolites
   * TEF scheme (relevant experimental endpoints, common mechanism of action, etc.)

4. HAZARD CHARACTERIZATION

   * experimental
   * epidemiologic

5. RISK ASSESSMENT STRATEGY

議事録（報告書）ドラフト（当日）
→これを元に討論、9月中に参加者から意見。
→10月初旬までに
まとめて、事務局へ

WHO Consultation on Risk Assessment of Non-dioxinlike PCBs
BgVV, Berlin, September 3 - 4, 2001

DAY 1

Welcome Addresss: Wolfgang Lingk, BgVV

Organizational/Administrative matters: Klaus-Erich Appel, BgVV

Overall Meeting Scope and election of chairman and rapporteur: Maged Younes, WHO

Introduction of Discussion Paper on PCB Risk Assessment, Martin van den Berg, University of Utrecht

Discussion (the following represents a synopsis of the day's major topics)

1. TERMINOLOGY

- The discussion involved what would be the most appropriate or accurate descriptor for the PCBs in question ('non-coplanar', 'non-dioxinlike', 'non-ortho substituted')
- functional vs. structural designations

- it was concluded that 'coplanar' and 'non-coplanar' were not appropriate definitions as even the non-ortho substituted PCBs weren't truly coplanar in configuration
- between non-dioxinlike and non-ortho substituted, the preferred definition was non-dioxin like as:

1) certain mono-ortho substituted PCBs have both dioxin-like and non-dioxinlike activity
2) a functional classification was used for the initial description of PCBs in the original WHO TEF scheme
3) changes to the congeners included in the first TEF scheme were the result of evolving scientific data.

2. EXPOSURE

a)

- the general conclusion was that commercial mixtures were not representative of environmental-based exposure scenarios
- additional toxicology studies were not considered relevant from a risk assessment perspective unless dealing with specific exposure scenarios (i.e., occupational, hazardous wastes, etc.)

- the usefullness of previous toxicology studies with commercial mixtures for current risk assessment strategies was thought to be limited
- recommendations were made that future studies, if necessary, involve reconstituted mixtures resembling relevant exposures

b)

- the question was raised if indicator congeners can serve as a useful indication of total PCB exposure.
- it was also discussed if indicator congeners can be used as hazard characterization surrogates.

It was concluded that with appropriate validation, indicator congeners could be used as an estimate of total PCB exposure. However, no current data exist to support the use of indicator congeners as a measure for toxicity.

c) external vs. internal dose measurements

- in general, for more persistent, bioaccumulative congeners, the internal measure associated with exposure would be the more appropriate dose metric
- it was also recognized that lower chlorinated non-dioxinlike PCBs may be capable of causing effects which would persist beyond measurable levels of the congener and, therefore, an external dose should be considered.

3. TOXICOLOGY

a) assessment of individual congeners

What are the most relevant/sensitive endpoints specific to non-dioxinlike PCBs?

- a number of endpoints were discussed (intracellular Ca^{2+} mobilization, PKC translocation, binding to the ryanodine receptor, induction of CYP2B/3A, estrogenicity, tumour promotion, neurotoxic effects (chemical, structural, functional), other endocrine-related effects (insulin, thyroid hormone).
- the general conclusion was that a number of the effects were cell line and/or species specific and/or could also be induced by dioxin-like chemicals
- a number of the different endpoints were found to have different dose-response relationships and different SARs for the same congener.
- it was considered that induction of CYP2B/3A plus indications of estrogenicity would be indicative of a nondioxin-like effect with the absence of CYP1A induction an indication of the lack of dioxin-like activity.
- one of the more sensitive endpoints, from an external dosing perspective, was the study of Rice and Hayward (1997) where nonhuman primate offspring exhibited neurobehaviour effects following exposure to an environmentally-relevant mixture of PCBs (breast milk) for 20 weeks following parturition; however, it was noted that the mixture also contained dioxin-like PCBs (PCBs 105, 118, 156, 157).
- additional information would be required to define a more precise relationship between degree of PCB congener chlorination and biological activity

- it was recognized that the U.S. EPA is currently involved with an assessment of noncancer effects associated with PCBs; comprehensive scientific database searches have been conducted and applicable data for hepatic, endocrine, immunologic, neurologic and reproductive effects compiled.
- as a number of these endpoints are relevant to an assessment of nondioxin-like PCBs, it was recommended WHO attempt to enter into a data sharing agreement with EPA as a future stage in their risk assesment of nondioxin-like PCBs
- additional similar data compilations will be required for for relevant endpoints not covered in the current EPA assessment (i.e, tumour promotion, carcinogenesis).
- for the latter effect, it was noted that the available studies with commercial mixtures indicate that nondioxin-like PCBs may be responsible for the tumourigenic response in ~~male animals~~ supportng the evidence from tumour promotion studies with nondioxin-like PCBs.
- future results should be available from the NTP chronic bioassay for PCB 153.

RECOMMENDATIONS

- The Consultation recognized that the level of exposure to non-dioxin-like PCBs has declined significantly over the last 25 years. This decline was due in part to a ban of the production and use of PCBs in industrialized countries. In addition general measures to limit the emissions of dioxin-like compounds and other environmental pollutants reduced the levels of non-dioxinlike PCBs in the environment. The Consultation agreed on the need for a survey of the available exposure data with respect to the ratio between non-dioxin-like PCBs and TEQs. One aim of such a survey would be to decide if the current regulation of TEQ exposure is regarded as sufficient for protection of humans against exposure to non-dioxinlike PCBs or if a separate regulation of the latter is still required e.g. for scenarios with relatively high exposure to non-dioxinlike PCBs such as via contaminated indoor air.

- Following the proposed toxicology data sharing exercise between WHO and EPA, a detailed evaluation will be conducted for those endpoints thought to be specific to nondioxin-like PCBs and the dose ranges for the NOELs/LOELs compared to estimated exposures. This process will also serve to identify those major areas of data requirements.