# CARCINOGENIC ASSESSMENT OF POLYCHLORINATED BIPHENYLS (PCBS) USING A NON-LINEAR DOSE-RESPONSE MODEL

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## Introduction

The Ontario Ministry of the Environment (OMOE) is currently reviewing the toxicological basis of its environmental standards for PCBs since most were developed over a decade ago and they do not reflect recent information on the toxicology and environmental fate of PCBs. Numerous adverse health effects have been documented for PCBs in animal and humans, including cancer and non-cancer effects[5]. This paper addresses the carcinogenic assessment of PCBs only.

PCBs have been shown to cause cancer in laboratory animals, but the evidence in humans is equivocal. Commercial PCB mixtures and, by inference, environmental PCB mixtures are classified as probably carcinogenic to humans (Group 2A) by the International Agency for Research on Cancer (IARC),[1] and the U.S. Environmental Protection Agency (U.S. EPA) (Group B2),[2] and are reasonably anticipated to be carcinogenic in humans according to the Report on Carcinogens published by The U.S. Department of Health and Human Services (NTP 2004).[3] While there is evidence indicating that PCBs are involved with the development of cancer, the underlying mechanism is not clear.[4] Several studies have suggested that PCBs can act as tumor promoters.[4,5,6] Despite the widespread recognition that PCB mixtures are probably carcinogenic to humans, few agencies have conducted quantitative assessments for this end-point

The U.S. EPA has proposed a revised approach for assessing cancer risk from environmental PCBs by considering both toxicity and environmental processes.[2,7,8] This approach uses results from animal studies conducted with commercial PCB mixtures to develop a range of human cancer potency estimates, and then considers the effect of environmental processes to determine appropriate values for representative classes of environmental mixtures. The U.S. EPA developed their cancer potency estimates based on data reported by Mayes *et al.*[9] on Sprague-Dawley rats exposed orally to four commercial PCB formulations (Aroclors 1016, 1242, 1254, and 1260). In their reassessment, U.S. EPA assumed a non-threshold approach to describe the observed carcinogenic response in test animals (*i.e.*, linear extrapolation).

However, there is convincing evidence to indicate that the mode(s) of action responsible for the carcinogenicity of PCBs is consistent with a non-genotoxic mechanism, possibly receptor-based, and hence with the presence of a biological threshold. This opinion is based on current findings indicating that PCB mixtures and selected individual congeners 1) are generally negative in *in-vitro* and *in-vivo* genotoxicity assays, 2) have significant promoting activity and negligible or equivocal initiating activity in various models of carcinogenesis, 3) display a threshold for promotion, and 4) induce cellular changes known to play a role in tumor promotion.[5,6] PCB mixtures have also been considered by the World Health Organization (WHO)[6] to have no significant genotoxic potential in humans.

In this study, we present the results of a carcinogenic assessment of PCBs using a non-linear (i.e., threshold) dose-response model.

## Materials and Methods

The critical bioassay data used by the U.S. EPA in their cancer reassessment was reported by Mayes *et al*.[9] Male and female Sprague-Dawley rats were exposed through diet over 2 years to individual Aroclor formulations (Aroclor 1260, 1254, 1242, and 1016). Liver hepatocellular adenomas and carcinomas in females were selected as the

critical endpoints. We re-evaluated the Mayes *et al*.[9]data as reported in US EPA[7] using the benchmark (BMD) dose-response model (USEPA, 2004, version 1.3.2[10]) to estimate threshold effects for this endpoint.

The exposure dose and the experimental results of Mayes *et al*.[9] for female rats used in the EPA reassessment and in the present analysis are shown in Table 1. Dietary rat exposure data were converted to equivalent human dose (EHD – mg/kg bw/day) using an allometric equation. The EHD normalized data was then modelled with the USEPA BMD software using both distribution and stochastic models. The distribution models included Log-logistic, Probit, Quantal-linear, Quantal-quadratic and Weibull; whereas the stochastic models included Gamma and Multistage. The lower 95% confidence limit was selected for the BMD analysis and the benchmark response was set at 0.1 (default value typically used in cancer bioassay data – USEPA, 2004[10]), resulting in an estimate corresponding to an increased incidence of liver tumourigenesis in rats of 10%. This value is consistent with the statistical power of the study of Mayes *et al*.[9] based on the number of control and treated animals. The output was the BMD corresponding to the 10% increased incidence of liver tumourigenesis ($BMD_{10}$) and the lower 95% confidence limit of the $BMD_{10}$ ($BMDL_{10}$). The resulting $BMD_{10}$ and the $BMDL_{10}$ values were evaluated by the statistical power of the curve fit as specified by USEPA[10].

Table 1 Incidence of Hepatocellular Adenomas and/or Carcinomas in Female Sprague-Dawley Rats Exposed to Aroclor Mixtures through the Diet for 2 Years (US EPA[2, 7], Mayes et al.[9])

| Aroclor | Administered dose(ppm) | Human equivalent dose (mg/kg bw-day) | No. of animals at termination | No. of animals with tumors[a] |
|---|---|---|---|---|
| control | 0 | 0 | 85 | 1 |
| 1016 | 50 | 0.72 | 48 | 1 |
| | 100 | 1.43 | 45 | 7 |
| | 200 | 2.99 | 50 | 6 |
| 1242 | 50 | 0.75 | 49 | 11 |
| | 100 | 1.53 | 45 | 15 |
| 1254 | 25 | 0.36 | 45 | 19 |
| | 50 | 0.76 | 49 | 28 |
| | 100 | 1.59 | 49 | 28 |
| 1260 | 25 | 0.35 | 49 | 10 |
| | 50 | 0.72 | 45 | 11 |
| | 100 | 1.52 | 50 | 24 |

[a]Tumors included hepatocellular adenomas and/or carcinomas

For each model, we estimated a toxicity reference value (TRV) that would be associated with no significant increase in carcinogenic effects under chronic exposure conditions. The $BMDL_{10}$ was considered the point of departure and, therefore, was corrected with uncertainty factors (UFs) in order to derive this TRV. In an attempt to reduce the subjectivity associated with UFs, we used the protocol developed by the Australian National Health and Medical Research Council(NHMRC)[11] specifically for deriving health-based guidelines for carcinogens from $BMDL_{10}$ values. A total UF of 1350 was obtained (2.5 for toxicodynamic interspecies variability, 10 for human variability, 3 for adequacy of the data base, 9 for malignant tumourigenesis, and 2 for equivocal genotoxicity). This UF was applied to the $BMDL_{10}$ to derive the TRVs.

**Results and Discussion**

Benchmark doses ($BMDL_{10}$) estimates obtained for the combined incidence of hepatocellular adenomas and carcinomas in female Sprague-Dawley rats ranged from 0.043 to 1.184 mg/kg bw-day for the 7 models tested. The log-logistic model produced the best fit of the data with statistical significance (Table 2) for all the four Aroclor formulations.

**Table 2** Comparative BMD and TRV Data for the Different Aroclor Formulations

| Aroclor | $BMD_{10}$ | $BMDL_{10}$ (mg/kg-bw/day) | TRV (µg/kg bw-day) |
|---|---|---|---|
| 1016 | 1.952 | 1.184 | 0.880 |
| 1242 | 0.330 | 0.224 | 0.170 |
| 1254 | 0.061 | 0.043 | 0.032 |
| 1260 | 0.200 | 0.146 | 0.110 |

Aroclor 1254 was the most potent (0.043 mg/kg bw-day), followed by Aroclor 1260 (0.146 mg/kg bw-day), Aroclor 1242 (0.224 mg/kg bw-day) and Aroclor 1016 (1.184 mg/kg bw-day). U.S. EPA also reported $BMD_{10}$ and $BMDL_{10}$ results (identified as $ED_{10}$ and $EDL_{10}$) using the same experimental data in their 1996 cancer reassessment [7,8]. We were able to successfully reproduce their results. The order of potency (1254 > 1260 » 1242 > 1016) resulted from our study is comparable to that reported by U.S. EPA. Using the $BMDL_{10}$ data and using a total UF of 1350, the estimated TRV was 0.88 µg/kg bw-day for Aroclor 1016, 0.17 µg/kg bw-day for Aroclor 1242, 0.032 µg/kg bw-day for Aroclor 1254, and 0.11 µg/kg bw-day for Aroclor 1260.

Given that Aroclor 1254 is the most potent, and human exposures to PCBs tend to be associated with the higher chlorinated congeners[7], it is proposed that the most appropriate TRV for carcinogenicity assessment would be 32 ng/kg bw-day. While this value is slightly higher than the RfD of 20 ng/kg bw-day established by U.S. EPA[2], the chronic MRL from the Agency for Toxic Substances and Disease Registry (ATSDR)[5], and the TDI recently proposed by WHO[6] for non-carcinogenic effects, it is not considered significantly different. Therefore, the TRV for non-carcinogenic effects recommended by U.S. EPA, ATSDR, and WHO of 20 ng/kg bw-day appears to be protective of carcinogenic effects based on the assumption of a non-linear dose-response relationship for this endpoint.

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