

Evaluation of the WWF -UK National Biomonitoring Survey 2003.

General:

This study, performed by the WWF and the University of Lancaster, offers some interesting data on the occurrence of selected persistent halogenated aromatic pollutants. It definitely gives a better insight in the occurrence in the general population of the UK. From an epidemiological point view it certainly has its limits due to the small number of volunteers studied at each location. However, as many human occurrence studies did not properly take into account various epidemiological aspects, it seems unfair towards the WWF to primarily focus on this aspect. This study should merely be considered as a preliminary 'range finding' study that could be followed up by a more detailed one. Such a future study might limit the number of locations and could give more attention to confounding and life style factors with an increase in number of subjects per location. In spite of these limitations, the present study does allow some evaluation or comparison with similar type of studies in other parts of the world. Answers to the specific questions asked to me by the Bromine Scientific Environmental Forum are given further below.

One major point of criticism on the report I would like to state on forehand is the fact that the authors continuously state that these compounds are (highly) toxic or hazardous and not even once include a proper assessment of the dose/concentration - response relationship for a given compound. This omission can not be excused by the fact that information about effects in humans is missing, as the WWF could have used the extensive scientific literature database containing both toxicokinetic and effect studies, e.g. for PCBs or DDT/DDE in rodents. By doing this and applying an appropriate safety factor the report would have stood out with others that have been produced during the last decade by environmental movements, which is irrespective of a positive or negative outcome. This would have avoided unscientific remarks such as in finding 1 like 'continue to pose unknown health risks' as it is theoretical impossible to state that there is a continuation of a risk, if a health risk is unknown.

Answers to the specific questions:

1. Looking at the findings of the Lancaster University study on "Organohalogen chemicals in human blood from around the United Kingdom", do you find the methodology used in the study

to be a good basis for accurately analysing the presence of chemical substances in human blood?

- a. Choice of volunteers and sampling methods
- b. Possibility to establish temporal trends
- c. Reliability of analytical methods
- d. Levels of detection used

(a) The choice of subjects and sampling methods are appropriate for a 'range finding' study as presented.

(b) Due to the low number of subjects and limited background info, any statements about temporal trends would merely be indicative, but these limitations are also recognized by the authors. However, singling out specific persons as done in appendix 2 and connecting them to a certain location is highly suggestive and improper use of the data without giving more specifics e.g. possibility of higher occupational exposure or caused by a strong deviation from average life style.

(c) The Lancaster University has a good reputation in the field of (analytical) environmental chemistry. At least in the report send to me, I could not find a proper description of the clean up procedure and analytical techniques used. Knowing the reputation of the lab I can hardly think that this is not available. The reliability of the analytical methods can not be judged properly as no description was included in the report, but only tables. In view of the often high levels of detection it is necessary to know if the authors e.g. used either EI or NCI GC-MS techniques. Were internal standards used, to calculate recovery after clean up or to determine individual responses on either GC-MS or GC-ECD? It is also important to know what the linear range was for the individual compounds and if this was acceptable for all compounds when analyzing these in one run at the same time.

(d) The limits of detection appear to be rather high for a number of compounds and this could be caused by the fact that the scientists had to work with relative small amounts of blood. For PCBs, other laboratories have achieved significantly lower detection limits using other biological or environmental matrices e.g. on GC-ECD. Nevertheless, the overall pattern of PCBs and their concentrations seem to be in line with other studies from a qualitative as well as quantitative point of view. The large inter-individual variation that is observed in this study is commonly seen and not unusual in these types of studies. I can not find a reference in the report related to the determination of the limits of detection. How many times the noise level has been

used by the laboratory? This is of particular importance for data of the deca-DPE. In this case the detection limit is several orders of magnitude higher than those found for other PBDEs. This is not surprising, as deca-DPE is notoriously difficult to analyze. Being not an analytical chemist, but merely a toxicologist with analytical experience, I think a proper evaluation of the used method should be made by an analytical chemist, who is familiar with the analysis of these specific compounds. I also like to point out that the limits of detections for deca-DPE are significantly above the levels that have been observed in occupationally exposed people based on lipid basis (Sjodin et al 2003).

2. Is it possible to establish an association between people's lifestyles and the levels of exposure to any chemical substances found in human blood as stated by the study?

Yes, it might be possible but would require a much more sophisticated study design using more parameters that included life style factors to avoid bias with confounding factors. More info would definitely be needed about various aspects of an individual's life compared with the personal info that has been collected in the present WWF study. I think involvement of an environmental epidemiologist in the planning stage of such a study would be prerequisite.

3. Looking at the levels of DecaBDE in human blood found by the UK study, do you think these levels present a risk to human health (comparison between the predicted no-effect level and the identified worst-case predicted exposure)? When stating that levels found are "low" or "high", to what reference do we compare?

With respect to risks of these Deca-PDE concentrations one has to rely on results from animal experiments. The neurobehavioral effects of Deca-DPE observed in a mice study by Viberg et al (2003) are the closest one can get to do any risk assessment. We have recently criticized this study (Vijverberg and Van den Berg 2004; Tox Sci in press). Assuming brain concentrations of this compound are responsible for the observed effects on a subtle developmental parameter, we noticed that these levels appear about three orders of magnitude higher than those observed in human blood c.q. milk in both background as well as occupational exposures. Based on these calculations we consider this study of limited relevance to risk assessment. If concentrations are indeed close or above 100 ng/g lipid in humans and it is assumed that there is similarity in the human brain on lipid basis, concentrations would be around two orders of magnitude lower than in the mice from the Viberg study. I would consider three orders of magnitude between human and

animal body burden as safe for this compound. Almost all individuals have this difference in order of magnitude if one assumes that the detection limit is the actual concentration (worst case). In practice one could expect for deca -DPE that concentrations in the brain would actual be lower than those observed in blood, milk or adipose tissue due to transport limitations of such a large molecule s as deca -DPE across the blood – brain barrier. However, if the margin in animal and human concentrations of Deca -DPE is found to be below two orders of magnitude , this should be considered as distinct warning signal keeping in mind that a safety factor 100 is commonly used for non genotoxic substances when extrapolating from animals to humans for risk assessment purposes. Thus, more information about the reliability of these samples by contra expertise and more human data from the UK is definitely necessary.

4. How do the levels found of Deca-BDE compare to the levels found of other chemicals in the same study?
 - a. Comparison between actual levels
 - b. Comparison of these levels to their predicted no-effect levels

(a) The observed concentrations of the Deca -DPE in those samples that are positive appear to be very high for background exposure if compared with the information from either Sjodin et al (2003) or the US (Environmental working group, www.ewg.org). The study by Sjodin et al. indicated that serum and breast milk in humans are rather comparable when compared on lipid basis. Thus, a first comparison between the US milk data and UK blood data shows that positive samples from the UK are often a factor 10 or higher than levels observed in the US. This is remarkable as information from North America indicates that the US background population has significantly higher body burden levels (Deca -DPE: 1-8 ng/g lipid milk; source: EWG) than that found in Europe. Clearly, the UK data for Deca -DPE appear to stand out. It is therefore of utter importance to collect more data on the UK population and perform a contra expertise of the positive samples by a laboratory with a lower detection limit for deca -DPE. The latter could confirm the incidental reported high levels of Deca-DPE in WWF -UK blood study

(b) See earlier comments given for question 3

5. Does a literature review of existing studies reveal:
 - a. Any indication of the number of chemicals present in human blood?

- b. To what extent the presence of a particular chemical in human blood is synonymous to an identified risk

(a) The number of xenobiotic compounds identified in the blood by itself does not say anything from a toxicological point of view but depends on the analytical techniques and associated detection limits. For a proper risk evaluation one needs to know the actual dose/concentration– response relationship, preferable for humans. The latter is usual unknown and consequently the risk assessor has to rely on animal data. By applying an appropriate safety factor, depending on the properties of the compound and relevant toxicological information, a safe dose or concentration can be determined for humans. In the case of PBDEs there seems to be little or no arguments to apply a safety factor other than 100 for (semi) chronic studies that involve developmental aspects in mammalian models.

In addition, the argument of mixture effects can be brought forward, but similar mechanism of actions between the compounds is often a prerequisite. In the case of PBDEs it is scientifically unsound to compare these e.g. PCBs when it involves a dioxinlike mechanism of action. In case of a proposed similar mechanism of action for neurotoxic effects between PCBs and PBDEs again there seems to be little or no evidence. For PCBs Seegal and co workers have established e.g. some distinct structure relationships depending on the number and position of the chlorine atoms. The studies done by Erikson and co workers do not show such a structure activity relationship. Those PBDEs that have been examined appear to have similar potencies in his model almost irrespective of the number and position of the bromine atoms. This is awkward and might indicate a non specific mode of action that is likely to be manifested only at higher (internal) dose levels, which might be unrealistic compared with background concentrations of exposure (See Letter to Editor Vijverberg and van den Berg). From mechanistic point of view there also seems to be no justification either to compare PBDEs with HBCDD or e.g. DDE/DDT. However, if all these compounds would be present at levels that are close to causing overt general toxicity, it can not be excluded that a mixture effect of more non specific toxic effects such as growth retardation, liver and kidney damage can occur. At present, there are obviously no indications that the observed levels of brominated flame retardants cause overt toxicity in humans. Thus, a specific mode of action by certain flame retardants causing effects at lower concentrations might be a clear reason for concern. So far, such specific modes of actions have not been identified in vivo for either PBDEs or HBCDD in contrast to e.g. dioxin like compounds (including the most toxicological relevant PCBs), DDE and organotins. This is in spite of the fact that

many research groups around the world are (almost desperately) searching for specific low level effects of these brominated flame retardants.

(b) Occurrence of given chemical in the human body is not synonym with a risk or effect, but depends on the concentration– effect relationship and associated lowest observed effect level. This is a basic principle in toxicology!

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