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Developmental Exposure to Mixtures of Persistent Environmental Pollutants with Focus on Bone and Retinoid System Modulations

Av

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AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen
vid Karolinska Institutet offentligen försvaras i
Samuelssonsalen, Tomtebodaväg 6, Solna

Torsdagen den 15 December, 2011, kl 09.30

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Stockholm 2011

ABSTRACT

Environmental pollution of Arctic regions has evoked a scientific as well as public concern. Arctic Inuit inhabitants consume large amounts of fatty fish and marine mammals and are therefore exposed to levels of environmental toxicants that are suspected to cause adverse health effects. Exposure to mixtures of environmental pollutants affects a wide range of clinical and biochemical parameters. Developing fetuses and infants are the most vulnerable groups to environmental contaminants. Experimental studies demonstrate that alterations of bone tissue and modulations in the retinoid system are considered as sensitive toxicological end-points. The present thesis is based on a one-generation toxicity study performed according to standard guidelines with enhancement to accommodate bone and retinoid system endpoints. Rats were exposed during gestation and lactation to two chemical mixtures: the Northern Contaminants Mixture (NCM) or the commercial mixture Aroclor 1254. The overall aim of the current work was to generate new experimental data, which will contribute new knowledge to improve the health risk assessment associated with the exposure to chemical mixtures with a focus on the postnatal consequences of the exposure during fetal life, using the situation of the Canadian Arctic populations as an example.

The body and organ weights, as well as serum levels of thyroid hormones and cholesterol were altered in young offspring at post-natal day (PND) 35 by perinatal exposure to the NCM or Aroclor 1254. In addition, levels of hepatic retinoids were decreased in the dams, as well as in their offspring at all post-natal follow-up time points following perinatal exposure to NCM or Aroclor 1254. Based on these findings, it was decided to perform both bone studies and more detailed retinoid studies.

Multiple bone parameters, including geometrical and biomechanical parameters, were clearly affected in the offspring at PND35 and partly affected at PND77, while no bone changes were detected at PND350 following perinatal exposure to NCM or Aroclor 1254. Affected parameters included reduced bone length, cross-sectional area, thickness and strength. None of these bone changes were observed in the dams after NCM or Aroclor 1254 exposure.

Results of detailed retinoid analysis demonstrated that retinol levels in liver were reduced in the dams and the offspring at PND35 and that, hepatic levels of the active metabolite of the retinoic acid were markedly reduced in the dams and the PND35 offspring after perinatal exposure to the NCM or Aroclor 1254. Reduction of retinyl palmitate levels in liver, as well as increase of retinol levels in kidney was observed in dams and their offspring at all time-points up to PND350 after perinatal exposure to NCM or Aroclor 1254. Results based on partial least square (PLS) analyses indicated that changes of different retinoid forms in livers induced by exposure to NCM or Aroclor 1254 were strongly associated with changes in body and liver weights, with alterations in levels of thyroid hormones, as well as with induction of liver cytochrome P450 activities.

Obtained results of alterations in bone and retinoid parameters are of relevance to dietary exposure situations, and this data may contribute to human health risk assessment by providing useful information for hazard characterization and exposure assessment. The generated data will be relevant not only for the Canadian Arctic population, but also for other populations with similar exposure profiles.

ISBN 978-91-7457-558-3