Phthalates increase the risk of allergies among children

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If the mother is particularly heavily exposed to phthalates during pregnancy, there is an increased risk of allergic asthma for the children. Credit: Fotosearch

Phthalates, which are used as plasticizers in plastics, can considerably increase the risk of allergies among children. This was demonstrated by

UFZ researchers in conjunction with scientists from the University of Leipzig and the German Cancer Research Center (DKFZ) in a current study published in the *Journal of Allergy and Clinical Immunology*. According to this study, an increased risk of children developing allergic asthma exists if the mother has been particularly heavily exposed to phthalates during pregnancy and breastfeeding. The mother-child cohort from the LINA study was the starting and end point of this translational study.

In our day-to-day lives, we come into contact with countless plastics containing plasticizers. These plasticizers, which also include the aforementioned phthalates, are used when processing plastics in order to make the products more flexible. Phthalates can enter our bodies through the skin, foodstuffs or respiration. "It is a well-known fact that phthalates affect our hormone system and can thereby have an adverse effect on our metabolism or fertility. But that's not the end of it," says UFZ environmental immunologist Dr Tobias Polte. "The results of our current study demonstrate that phthalates also interfere with the immune system and can significantly increase the risk of developing allergies."

At the outset of the study, the team of UFZ researchers examined the urine of pregnant women from the LINA (lifestyle and environmental factors and their influence on the newborn-allergy-risk) mother-child cohort study and searched for metabolites of phthalates. The concentration level determined in each case was found to correlate with the occurrence of allergic asthma among the children. "There was a clearly discernible relationship between higher concentrations of the metabolite of benzylbutylphthalate (BBP) in the mother's urine and the presence of allergic asthma in their children", explains Dr Irina Lehmann, who heads the LINA study.

Researchers were able to confirm the results from the mother-child cohort in the mouse model in collaboration with colleagues from the

Medical Faculty at the University of Leipzig. In this process, mice were exposed to a certain phthalate concentration during pregnancy and the lactation period, which led to comparable concentrations of the BBP metabolite in urine to those observed in heavily exposed mothers from the LINA cohort. The offspring demonstrated a clear tendency to develop allergic asthma; even the third generation continued to be affected. Among the adult mice, on the other hand, there were no increased allergic symptoms. "The time factor is therefore decisive: if the organism is exposed to phthalates during the early stages of development, this may have effects on the risk of illness for the two subsequent generations," explains Polte. "The prenatal development process is thus clearly altered by the phthalate exposure."

Phthalates turn off regulatory genes

In the course of the LINA mother-child cohort study, UFZ scientists investigated the lifestyle and environmental factors of pregnant women and their influence on the allergy risk of infants. Credit: UFZ/André Künzelmann

In order to establish precisely what may have been modified, Polte and his team, in collaboration with colleagues from the German Cancer Research Center (DKFZ), took a close look at the genes of the young mice born to exposed mothers. So-called methyl groups were found in the DNA of these genes – and to a greater extent than is usually the case. In the course of this so-called epigenetic modification of the DNA, methyl groups attach themselves to a gene like a kind of padlock and thus prevent its code from being read, meaning that the associated protein cannot be produced. After the researchers treated the mice with a special substance intended to crack the methyl "locks" on the affected genes, the mice demonstrated fewer signs of allergic asthma than before. Dr Polte concludes the following: "Phthalates apparently switch off decisive genes by means of DNA methylation, causing the activity of these genes to be reduced in the young mice."

But which genes cause allergic asthma if they cannot be read? So-called T-helper 2 cells play a central part in the development of allergies. These are kept in check by special opponents (repressors). If a repressor gene cannot be read as a result of being blocked by methyl groups, the T-helper 2 cells that are conducive to the development of allergies are no longer sufficiently inhibited, meaning that an allergy is likely to develop. "We surmise that this connection is decisive for the development of allergic asthma caused by phthalates," says Polte. "Furthermore, in the cell experiment, we were able to demonstrate that there is an increased formation of T-helper 2 cells from the immune cells of the offspring of exposed mother mice than is the case for the offspring of non-exposed

animals. This enabled us to establish an increased tendency towards allergies once again."

From humans to mice and back again

In mice, the researchers were able to prove that a repressor gene that has been switched off due to DNA methylation is responsible for the development of allergic asthma. But does this mechanism also play a part in humans? In order to answer this question, the researchers consulted the LINA cohort once more. They searched for the corresponding gene among the children with allergic asthma and studied the degree of methylation and gene activity. Here, too, it became apparent that the gene was blocked by methyl groups and thus could not be read. "Thanks to our translational study approach – which led from humans via the mouse model and cellular culture back to humans again – we have been able to demonstrate that epigenetic modifications are apparently responsible for the fact that children of mothers who had a high exposure to phthalates during pregnancy and breastfeeding have an increased risk of developing allergic asthma," says Polte. "The objective of our further research will be to understand exactly how specific phthalates give rise to the methylation of genes which are relevant for the development of allergies."

More information: Susanne Jahreis et al. Maternal Phthalate Exposure Promotes Allergic Airway Inflammation over Two Generations Via Epigenetic Modifications, *Journal of Allergy and Clinical Immunology* (2017). DOI: 10.1016/j.jaci.2017.03.017

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