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MnHexP: Background information on the detection of the degradation product of a plasticizer in urine samples

The State Agency for Nature, Environment and Consumer Protection of North Rhine-Westphalia (LANUV) has detected mono-n-hexyl phthalate (MnHexP) in a follow-up analysis of older urine samples from children. This substance could be a metabolite from various phthalates, such as dihexyl phthalate, decylhexyl phthalate or certain other mixed-chain phthalates, or can be directly taken up in the form of hexyl hydrogen phthalate.

Phthalates are chemical compounds that are mainly used as plasticisers in plastics such as PVC. However, the phthalates are not firmly bound in the respective plastics, but can be released from them. As phthalates are produced and used in large quantities, they can be detected almost ubiquitously in the environment (soil, water, air).

Triggered by a suspected case, the LANUV subsequently examined urine samples that are regularly collected from children aged 2 to 6 years in North Rhine-Westphalia as part of its human biomonitoring study (HBM). As a result, the substance MnHexP was detected considerably more frequently and in higher concentrations in urine samples collected more recently when compared to older samples: when urine samples from 2020/21 were examined, MnHexP was detected in 61% of the samples, but only in 26% of the samples from the period 2017/18. The measured concentrations also increased significantly: On average, they were at 0.28 micrograms per liter in samples from 2017/18 and at 2.09 micrograms per liter in samples from 2020/21.

In initial evaluations of urine samples currently being sampled as part of the 6th German Environmental Health Study (GerES VI), the Federal Environment Agency (UBA) has also detected the substance in more than a third of the urine samples taken so far from adults aged between 18 and 79. These data are still preliminary, as only some of the samples have been taken and evaluated.

The products or sources responsible for the currently observed occurrence of this substance in the urine samples are currently not known. It is also not clear to

which of the possible precursors the presence of MnHexP in urine can be attributed.

Di-n-hexyl phthalate as a possible precursor was examined in 226 foodstuffs as part of the [BfR MEAL study](#). All analytical results were below the respective limit of detection. The use of di-n-hexyl phthalate is prohibited in plastic food contact materials such as food packaging and in cosmetic products. Based on animal studies, the possible precursor compounds are considered reprotoxic (i.e. toxic to reproduction). However, it is important to note that the presence of a metabolite in urine indicates exposure, but not whether there is an immediate health risk. However, due to the reprotoxic properties of both MnHexP and its possible precursors, the intake of these substances should be reduced as much as possible.

Most of the possible precursor substances in question are also subject to strict use restrictions throughout Europe. For example, they have been identified as substances of very high concern under the EU chemicals regulation REACH. In addition, further regulatory activities are planned by the European Chemicals Agency (ECHA). The responsible Federal Environment Agency and the ECHA are currently trying to identify the source of the findings.

1 Background

The German Federal Institute for Risk Assessment (BfR) reports on the regulatory status of phthalates that may form the metabolite mono-n-hexyl phthalate (MnHexP). This metabolite was detected in 61% of urine samples taken from a cohort of 250 children in 2020/21 as part of human biomonitoring (HBM). In contrast, samples taken from children between 2015 and 2018 rarely contained MnHexP and only to a minor extent. In comparable measurements of urine samples from more than 500 adults taken in 2023, MnHexP was detected in more than a third of the samples. MnHexP was also found in samples from Denmark. MnHexP could not be detected in samples from the Federal Environmental Specimen Bank, the most recent sample of which was taken in January 2020.

Substances that may lead to the presence of mono-n-hexyl phthalate in urine samples

- **Hexyl hydrogen phthalate (IUPAC name: mono-n-hexyl phthalate)**, MnHexP
EC 246-302-8, CAS 24539-57-9
- **Di-n-hexyl phthalate**, DnHexP
EC 201-559-5, CAS 84-75-3, CLP index no. 607-702-00-1¹,
- **1,2-Benzenedicarboxylic acid, di-C6-10-alkyl ester**
EG 271-094-0, CAS 68515-51-5
- **1,2-Benzenedicarboxylic acid, dihexyl ester**, branched and linear
EC 271-093-5, CAS 68515-50-4, CLP index no. 607-710-00-5
- **1,2-Benzenedicarboxylic acid, mixed decyl, hexyl and octyl diesters**
EG 272-013-1, CAS 68648-93-1
- **1,2-Benzenedicarboxylic acid, mixed hexyl-, oleyl- and stearyl diesters**
EG 284-662-8, CAS 84961-72-8
- **Decylhexyl phthalate**
EG 247-210-0, CAS 25724-58-7
- Reaction mass of butyl decyl phthalate and decyloctyl phthalate and dicyclohexyl phthalate and **dihexyl phthalate** and diisooctyl phthalate
EG 904-803-5, CAS -
- Alcohols, C6-13, mixed with **di-C6-13 alkyl phthalates**
EG 271-229-3, CAS 68526-81-8

2 Result

The use of many phthalates is banned or strictly regulated in the European Union under European chemicals legislation.

The REACH Regulation (EC) No. 1907/2006 regulates the registration, assessment, authorization and restriction of chemicals in the EU, and the CLP Regulation (EC) No. 1272/2008 regulates the classification, labelling and packaging of hazardous substances. Currently, no registration is active under REACH for any of the above substances.

¹ In Annex VI of Regulation (EC) 1272/2008 (CLP Regulation)

2.1 Measures taken to date under the CLP Regulation/REACH Regulation

The substances **1,2-benzenedicarboxylic acid, dihexyl ester, branched and linear** (EC number 271-093-5, CAS number 68515-50-4, index number 607-710-00-5), and **dihexyl phthalate** (EC number 201-559-5, CAS number 84-75-3, index number 607-702-00-1) as well as the substance group **1,2-benzenedicarboxylic acid, di-C6-10-alkyl ester** (EC number 271-094-0, CAS number 68515-51-5), and **1,2-benzenedicarboxylic acid, mixed decyl, hexyl and octyl diesters** (EC number 272-013-1, CAS number 68648-93-1) with ≥ 0.3 % dihexyl phthalate, are classified as **toxic for reproduction (category 1B, H360FD)** according to the CLP Regulation and were included in REACH Annex XIV based on REACH Art. 57c. Substances listed in REACH Annex XIV are subject to authorisation (see below).

Furthermore, phthalates classified as reproductive toxicants (CLP category Repr. 1B) may not be used as substances, as constituents of other substances or in mixtures for supply to the general public according to entry 30 in REACH Annex XVII if the individual concentration of the substance or mixture exceeds certain limit values.

2.2 Planned measures under the CLP Regulation/REACH Regulation

At the meeting of the risk management expert group (RiME+, Risk Management and Evaluation, an exchange forum of the REACH Member State competent authorities, ECHA and representatives of the EU Commission on risk management planning) in Paris in October 2023, the EU Commission and ECHA presented updated plans for the so-called "Restriction Roadmap" for planned restriction projects under the REACH Regulation. This roadmap is to be discussed in March 2024 following a review by the competent national authorities.

A **restriction** according to Article 69 (2) of the REACH Regulation of phthalates **in products** is planned after the expiry date for authorisation according to the EU Commission's rolling list of restrictions. It is not expected that the corresponding request from the EU Commission to ECHA and notification to the Registry of Intentions (RoI) will be expressed before the fourth quarter of 2025.

According to the EU Commission's updated "Restriction Roadmap", France is preparing a group entry for C4-C6 phthalates and intends to submit a proposal for classification in 2024. The opinion of the Risk Assessment Committee will be available in September 2025 at the earliest.

2.3 Assessment from a REACH perspective on the detection of MnHexP

Based on the available information, ECHA (described in ECHA's analytical report GMT 134) sees a need for (further) regulatory risk management at EU level - ECHA explicitly provides for a **restriction in combination with an authorisation** for all ortho-phthalates with substituents of medium chain length (C4 - C6).

In contrast, ECHA currently sees no need for regulatory risk management at EU level for non-registered substances (or those with inactive registrations) such as ortho-phthalates with substituents of medium chain length (vastly C7 - C8) that contain di-n-hexyl phthalate (DnHexP) or can release MnHexP. Excluded from this are restriction activities according to Article 69(2) for **1,2-benzenedicarboxylic acid, di-C6-10-alkyl ester** (EC no. 271-094-0, CAS no. 68515-51-5) and **1,2-benzenedicarboxylic acid, mixed decyl, hexyl and octyl diesters** (EC no. 272-013-1, CAS no. 68648-93-1) with ≥ 0.3 % dihexyl phthalate.

Phthalates that have been identified as substances of very high concern and included in the so-called candidate list are subject to the obligation to notify the ECHA in accordance with Article 7(2) of the REACH Regulation. Substances on this candidate list are to be successively included in Annex XIV of the REACH Regulation, the list of substances subject to authorisation, and replaced in the long term by less hazardous alternatives. Industry will then have to submit an application for authorisation for the manufacture and use of such substances in the EU. Substances subject to authorisation may only be used within the EU if they have been authorised by the EU Commission. However, imported products are not affected by the authorisation requirement. Therefore, a probable source leading to the findings of MnHexP cannot be identified from REACH data.

3 Risk management options, Recommended measures

As an option for minimising MnHexP until a **restriction** under **Article 69(2)** of the REACH Regulation comes into effect, it could be examined whether and, if so, which products could be a source of phthalates that can release mono-n-hexyl phthalate.

ECHA's proposal (GMT 134) to investigate how best to elucidate the composition of registered ortho-phthalates with substituents of medium chain length (vastly C7 - C8), specifically to determine whether classified constituents or ortho-phthalates with linear C6 chain are present, is supported by BfR.

The BfR also recommends that phthalates, which can release mono-n-hexyl phthalate as a metabolite, be addressed as part of the European PARC initiative. PARC is the European Partnership for the Assessment of Risks from Chemicals, which includes over 200 partners from 28 countries and three EU authorities (the European Chemicals Agency (ECHA), the European Environment Agency (EEA) and the European Food Safety Authority (EFSA)). The BfR, like the Federal Environment Agency, is involved in various PARC work packages.

Further information on the BfR website:

Questions and answers about phthalates (only available in German)

https://www.bfr.bund.de/de/fragen_und_antworten_zu_phthalat_weichmachern-186796.html

Information about PARC

https://www.bfr.bund.de/en/partnership_for_the_assessment_of_risk_from_chemicals_parc-313567.html

About the BfR

The German Federal Institute for Risk Assessment (BfR) is a scientifically independent institution within the portfolio of the Federal Ministry of Food and Agriculture (BMEL) in Germany. The BfR advises the Federal Government and the States ('Laender') on questions of food, chemicals and product safety. The BfR conducts independent research on topics that are closely linked to its assessment tasks.

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