Improving the chemical safety of food contact articles
-
Food Packaging Forum's Work in 2019

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SATIRICAL CONTRIBUTION

Satirical contribution: Non-linear endocrine no-dose effects—towards a new paradigm in toxicology

I. M. Portant · R. E. Sults

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Adverse health effects of endocrine-disrupting chemicals are controversially discussed. While scientists still debate about the potential existence of so-called low-dose effects, we here present evidence that health risks resulting from exposure below the low-dose level might have been overlooked so far. Here, for the first time, biological consequences of exposure to an endocrine disruptor at the no-dose level are presented. This will induce a seismic shift in toxicological paradigms and risk assessment.

The pesticide and suspected endocrine disrupter hypochondriazole was used as a model compound. First, endocrine properties of the compound were tested in vivo in the mussel species *Gastropoda artifaciens*. Treatment with four different batches of hypochondriazole greatly inhibited mussel growth (Fig. 1a). Subsequently, effects of hypochondriazole on estrogen receptor-dependent signaling were assessed in an in vitro reporter gene assay. These analyses demonstrated the presence of a strong non-linear no-dose effect on estrogen-dependent signaling (Fig. 1b). When extrapolating the data towards concentrations below zero, it becomes obvious that at concentrations smaller than -10 M detrimental effects of hypochondriazole on estrogen-dependent processes should be expected due to the exponentially rising no-dose–response curve (Fig. 1b).

To further substantiate these in vitro data, a PLP (poor laboratory practice)-compliant 2-year carcinogenicity study was performed in rats. After sacrifice, the animals were analyzed for the presence of tumors and the correlation of tumor incidence and administered dose of hypochondriazole was investigated. As depicted in Fig. 1c, a clear-cut dose-dependent increase of tumor burden was observed. Histological inspection of tissues revealed pronounced substance-induced alterations (Fig. 1d).

The mechanism by which hypochondriazole interferes with mammalian cells was further assessed using liver samples from the above animal study in combination with an unbiased integrated molecular systems multi-bullshitomics approach. Extensive data mining revealed that specific biological processes were significantly perturbed upon exposure of rats to hypochondriazole (Table 1). Of note, similar processes have been shown to be deregulated in various human tumor entities (own unpublishable information), meaning that hypochondriazole should be regarded as a potent tumor inducer also in humans.

Altogether, the presented data suggest that exposure even below the level of zero can result in severe impairment of human health. An immediate ban of all types of chemical entities is, therefore, highly recommended. In addition, the

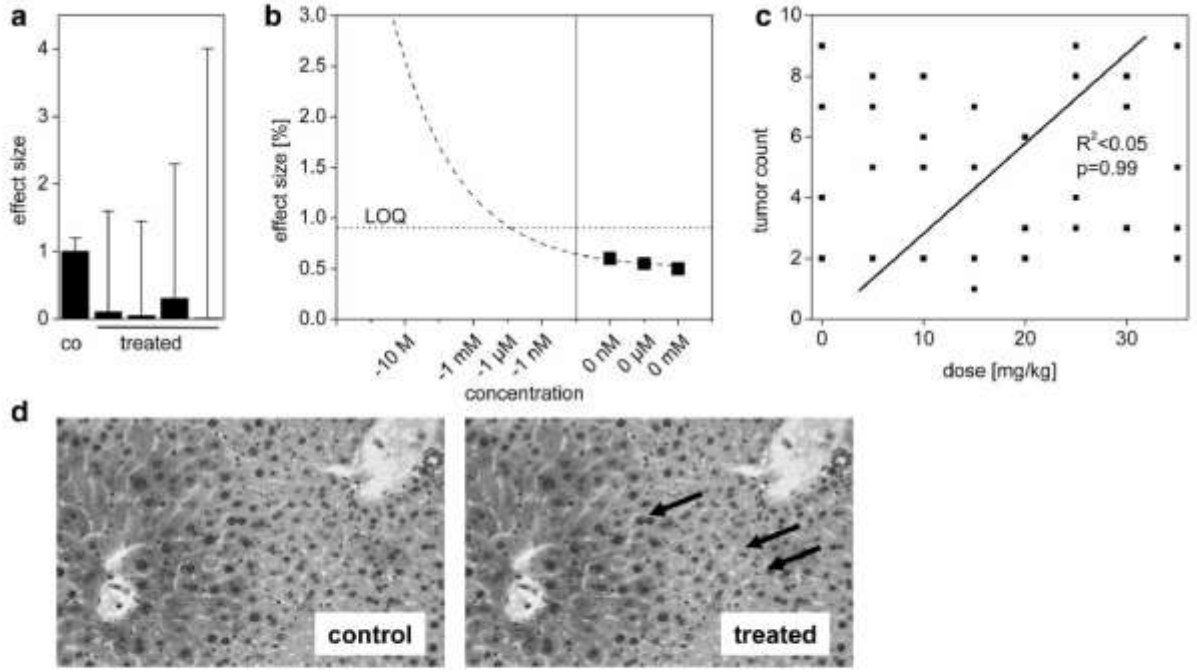

Fig. 1 Effects of hypochondriazole on endocrine functions and tumor growth. **a** Bar chart of *Gastropoda artifaciens* mussel growth following exposure to four different batches of hypochondriazole. Mean +SD of $n=25$ (control) or $n \leq 1$ (treated) individuals is shown. **b** Demonstration of a non-linear no-dose effect of hypochondriazole in an estrogen receptor-driven luciferase assay. The dashed line indicates the deduced no-dose–response curve. *LOQ* limit of quantitation. **c** Hypochondriazole dose-dependently induces tumors in rats in a 2-year carcinogenicity study. Tumor counts for each individual animal ($n=3$–4 rats per dose group) are given. **d** Histological comparison of control (left) and hypochondriazole-treated rat liver tissue (right). Arrows indicate lesions

Table 1 Bioinformatic data mining reveals de-regulation of biochemical functions in hypochondriazole-treated rat livers

Biological function	*P* value
Gene expression	<0.00000000000000000000000000000001
Metabolism	<0.00000000000000000000000000000001
Signaling	<0.00000000000000000000000000000001
Cellular processes	<0.00000000000000000000000000000001
Photosynthesis	<0.00000000000000000000000000000001

observed non-linear no-dose effect makes it necessary to also prohibit the absence of hazardous material.

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Compliance with ethical standards

Conflict of interest The authors declare that they have conflicts but no interests.

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EDITORIAL

Satirical contributions in toxicology

Hermann M. Bolt[1] · **Jan G. Hengstler**[1]

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Until recently, the editors of the *Archives of Toxicology* did not think that a satirical section had a place among the pages of a serious scientific journal. However, our opinions were immediately and unanimously altered upon receiving the exceptional contribution of I. M. Portant and R. E. Sults from Awkward Medical School (Portant and Sults 2019). The formalities were taken care of posthaste, and we are now pleased to announce the start of a new section in our journal that provides a platform for distinguished toxicologists to share their opinions and wisdom—even making use of the age-old art form of satire. One formal requirement is that the authors inform us if and when their real names may be revealed, e.g. after retirement, or as requested in the present case, after the passing of the distinguished authors. The outstanding contribution of I. M. Portant and R. E. Sults is a must-read, not only for experts in the field of endocrine disruption, but for all of us who relentlessly pursue scientific truth in our areas of research. Enjoy.

Commentary

A Section 508–conformant HTML version of this article is available at https://doi.org/10.1289/EHP644.

Scientific Challenges in the Risk Assessment of Food Contact Materials

Jane Muncke,[1] Thomas Backhaus,[2] Birgit Geueke,[1] Maricel V. Maffini,[3] Olwenn Viviane Martin,[4] John Peterson Myers,[5,6] Ana M. Soto,[7] Leonardo Trasande,[8] Xenia Trier,[9] and Martin Scheringer[10,11]

[1]Food Packaging Forum Foundation, Zurich, Switzerland
[2]Department of Biological & Environmental Sciences, University of Gothenburg, Sweden
[3]Independent Consultant, Germantown, Maryland, USA
[4]Institute for the Environment, Brunel University London, Uxbridge, UK
[5]Environmental Health Sciences, Charlottesville, Virginia, USA
[6]Department of Chemistry, Carnegie Mellon University, Pittsburg, Pennsylvania, USA
[7]Department of Integrative Physiology and Pathobiology, Tufts University School of Medicine, Boston, Massachusetts, USA
[8]Department of Pediatrics, New York University School of Medicine, New York, New York, USA
[9]DTU Food, Technical University of Denmark, Copenhagen, Denmark (currently at European Environmental Agency, Copenhagen, Denmark)
[10]Research Centre for Toxic Compounds in the Environment, Masaryk University, Brno, Czech Republic
[11]Institute for Chemical and Bioengineering, Swiss Federal Institute of Technology (ETH), Zurich, Switzerland

Background: Food contact articles (FCAs) are manufactured from food contact materials (FCMs) that include plastics, paper, metal, glass, and printing inks. Chemicals can migrate from FCAs into food during storage, processing, and transportation. Food contact materials' safety is evaluated using chemical risk assessment (RA). Several challenges to the RA of FCAs exist.

Objectives: We review regulatory requirements for RA of FCMs in the United States and Europe, identify gaps in RA, and highlight opportunities for improving the protection of public health. We intend to initiate a discussion in the wider scientific community to enhance the safety of food contact articles.

Discussion: Based on our evaluation of the evidence, we conclude that current regulations are insufficient for addressing chemical exposures from FCAs. RA currently focuses on monomers and additives used in the manufacture of products, but it does not cover all substances formed in the production processes. Several factors hamper effective RA for many FCMs, including a lack of information on chemical identity, inadequate assessment of hazardous properties, and missing exposure data. Companies make decisions about the safety of some food contact chemicals (FCCs) without review by public authorities. Some chemical migration limits cannot be enforced because analytical standards are unavailable.

Conclusion: We think that exposures to hazardous substances migrating from FCAs require more attention. We recommend *a*) limiting the number and types of chemicals authorized for manufacture and *b*) developing novel approaches for assessing the safety of chemicals in FCAs, including unidentified chemicals that form during or after production. https://doi.org/10.1289/EHP644

Food Packaging Forum

The Food Packaging Forum enables stakeholders to generate knowledge based on scientific facts, so they can make changes that result in a better protection of public and environmental health.

FPF Team
Justin Boucher
Birgit Geueke
Ksenia Groh
Phoenix Jieh
Richard Mikosch
Jane Muncke

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Martin Scheringer

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FPF is communicating (and generating) scientific knowledge

- Bi-weekly newsletter with information from science, regulation, industry.
- Dossiers on selected relevant topics, e.g. NIAS, BPA, etc.
- Webinars on e.g.
  - “Food additives and child health”
  - “Prioritization of potential genotoxicants in FCMs”
  - “Chemicals in plastics: chemicals and composition”
- Participation in and organization of conferences and workshops
- 26 presentation in 2019. On foodpackaging and FCM related concepts, knowledge, issues. To scientific audiences, regulators, industries, the general public.
- Participation in and organization of scientific research projects

ABOUT THE CONFERENCE

Throw-away plastics and food packaging don't just harm turtles and whales. They can contain a toxic soup of chemicals that can threaten each of us and our families. *That makes it personal.*

The **UNWRAPPED** conference will bring together world-renowned scientists with leaders in public health protection, plastic pollution advocacy, and solutions-oriented companies.

The **UNWRAPPED** conference is part of Plastic Exposed, an international project working to increase global recognition of the known human health risks of plastic and other single-use food packaging and promote a culture shift to safer reusable alternatives.

Meet the organizations and foundations who are behind **Plastic Exposed** and **UNWRAPPED**.

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PLASTIC HEALTH SUMMIT

HOW TO TAKE CARE OF THE NEXT GENERATION?

ZonMw PLASTIC HEALTH COALITION PLASTIC SOUP FOUNDATION


PLASTIC
SOUP

HCPP – Hazardous Chemicals in Plastic Packaging

- Funded by the MAVA Foundation
- Finished in 2019
- 7 international partners
- Cats herded by FPF

https://www.foodpackagingforum.org/hcpp-project

HCPP – Hazardous Chemicals in Plastic Packaging

- Collection of information of plastic-associated chemicals.
- Collection of supporting (eco)toxicological data.
- Hazard-based grouping.
- Detailed assessment of phthalates as a group of plastic-associated chemicals that are potentially relevant for human health and the environment.
- Analysis of the economic contexts and substitution options.

https://www.foodpackagingforum.org/hcpp-project

HCPP – Hazardous Chemicals in Plastic Packaging

Food Packaging Forum

September 2018

Prioritization approaches for hazardous chemicals associated with plastic packaging

Birgit Geueke[1], Pedro A. Inostroza[2], Maricel Maffini[3], Thomas Backhaus[2], Bethanie Carney-Almroth[2], Ksenia J. Groh[1], and Jane Muncke[1]

[1]Food Packaging Forum Foundation, Zurich, Switzerland
[2]Department of Biological and Environmental Sciences, University of Gothenburg, Gothenburg, Sweden
[3]Independent Consultant, Germantown, MD, USA

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HCPP – Hazardous Chemicals in Plastic Packaging

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journal homepage: www.elsevier.com/locate/scitotenv

Review

Overview of known plastic packaging-associated chemicals and their hazards

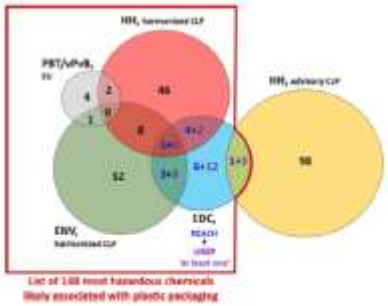
Ksenia J. Groh [a,*], Thomas Backhaus [b], Bethanie Carney-Almroth [b], Birgit Geueke [a], Pedro A. Inostroza [b], Anna Lennquist [c], Heather A. Leslie [d], Maricel Maffini [e], Daniel Slunge [f], Leonardo Trasande [g], A. Michael Warhurst [h], Jane Muncke [a]

[a] Food Packaging Forum Foundation, Zurich, Switzerland
[b] Department of Biological and Environmental Sciences, University of Gothenburg, Gothenburg, Sweden
[c] International Chemical Secretariat (ChemSec), Gothenburg, Sweden
[d] Department of Environment & Health, Vrije Universiteit Amsterdam, the Netherlands
[e] Independent Consultant, Germantown, MD, USA
[f] Centre for Sustainable Development (GMV), University of Gothenburg, Gothenburg, Sweden
[g] School of Medicine, New York University, New York, USA
[h] CHEM Trust, London, United Kingdom

HIGHLIGHTS

- Database of Chemicals associated with Plastic Packaging (CPPdb) is presented.
- CPPdb contains chemicals used in manufacturing and/or present in final articles.
- 906 chemicals identified as likely, 3377 chemicals as possibly associated.
- Hazard data: CLP classifications, EDC, PBT, vPvB identifications explored.
- Data gaps concerning both the use and toxicity of numerous substances identified.

GRAPHICAL ABSTRACT

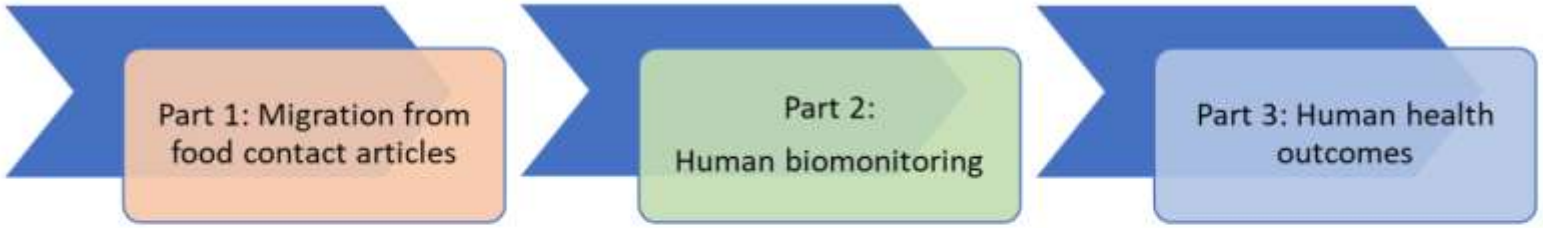


HCCH – Food Contact Chemicals and Human Health

- 3 international core partners
- Again, FPF is leading the team
- 2018-2019

https://www.foodpackagingforum.org/resources/research-projects/fcch-project

HCCH – Food Contact Chemicals and Human Health



Part 1:

- What FCCs are known to be used/authorized for use in food contact materials (FCMs) and articles (FCAs)?
- For which FCCs is there evidence for migration and/or extraction from FCMs and FCAs?

Part 2:

- For which FCCs is there evidence for human exposure from biomonitoring studies?

Part 3:

- How are FCCs that humans are exposed to associated with adverse human health outcomes?

https://www.foodpackagingforum.org/resources/research-projects/fcch-project

HCCH – Food Contact Chemicals and Human Health

December 23, 2018

Other Open Access

Protocol for a systematic map of the evidence of migrating and extractable chemicals from food contact articles

Martin, Olwenn V.; Geueke, Birgit; Groh, Ksenia J.; Chevrier, Jonathan; Fini, Jean-Baptiste; Houlihan, Jane; Kassotis, Christopher; Myers, Pete; Nagel, Susan C.; Pelch, Katherine E.; Sargis, Robert M.; Trasande, Leonardo; Vandenberg, Laura N.; Wagner, Martin; Maffini, Maricel V.; Muncke, Jane

Protocol for a systematic map of the evidence of migrating and extractable chemicals from food contact articles

https://www.foodpackagingforum.org/resources/research-projects/fcch-project

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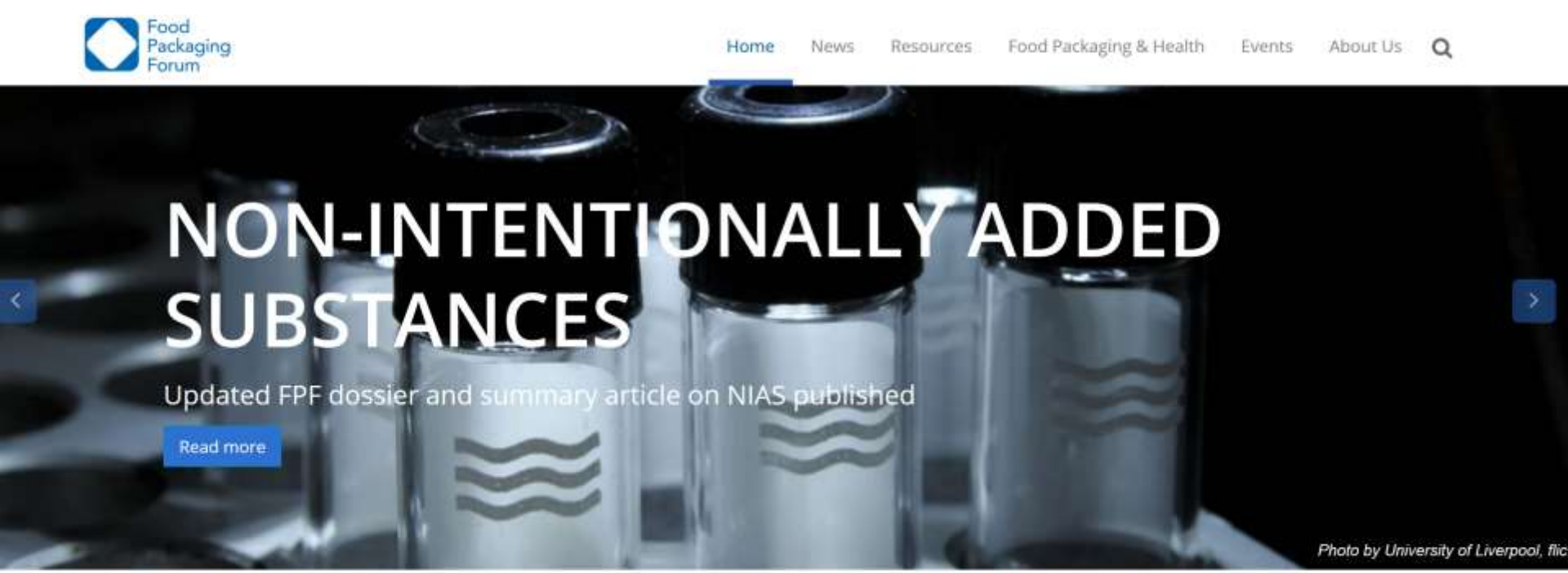

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