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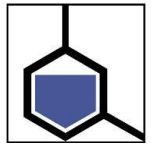

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Regulatory Safety – Spurring Innovation for Safer Alternatives

CIEX – Chemical Innovation Exchange

Frankfurt, 9./10. October 2019

Dr. Rainer Otter

1998: ~ 20 Years Ago: Toys and Childcare Articles

EU Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE)

Phthalate migration from soft PVC toys and child-care articles

Opinion expressed at the CSTEE third plenary meeting Brussels, 24 April 1998

L 315/46 EN Official Journal of the European Communities 9. 12. 1999

COMMISSION DECISION

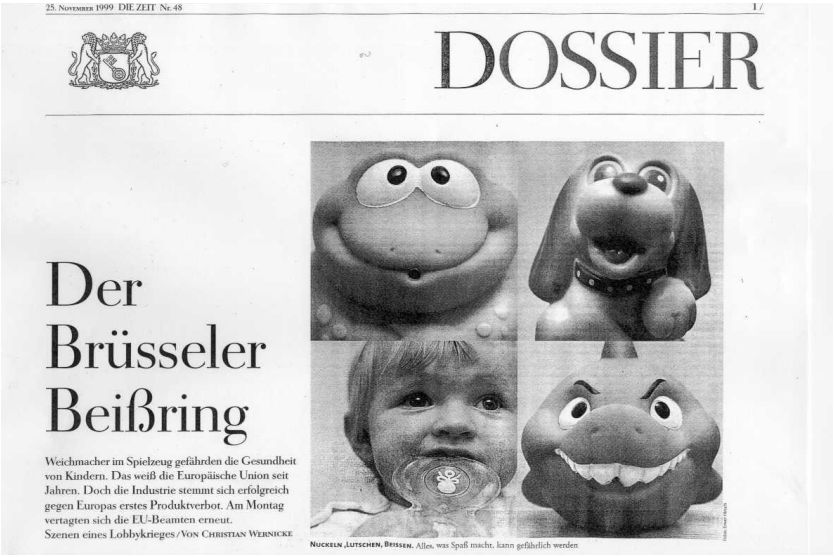
of 7 December 1999

adopting measures prohibiting the placing on the market of toys and childcare articles intended to be placed in the mouth by children under three years of age made of soft PVC containing one or more of the substances di-iso-nonyl phthalate (DINP), di(2-ethylhexyl) phthalate (DEHP), dibutyl phthalate (DBP), di-iso-decyl phthalate (DIDP), di-n-octyl phthalate (DNOP), and butylbenzyl phthalate (BBP)

(notified under document number C(1999) 4436)

(Text with EEA relevance)

(1999/815/EC)



25. November 1999 DIE ZEIT Nr. 48

DOSSIER

Der Brüsseler Beißring

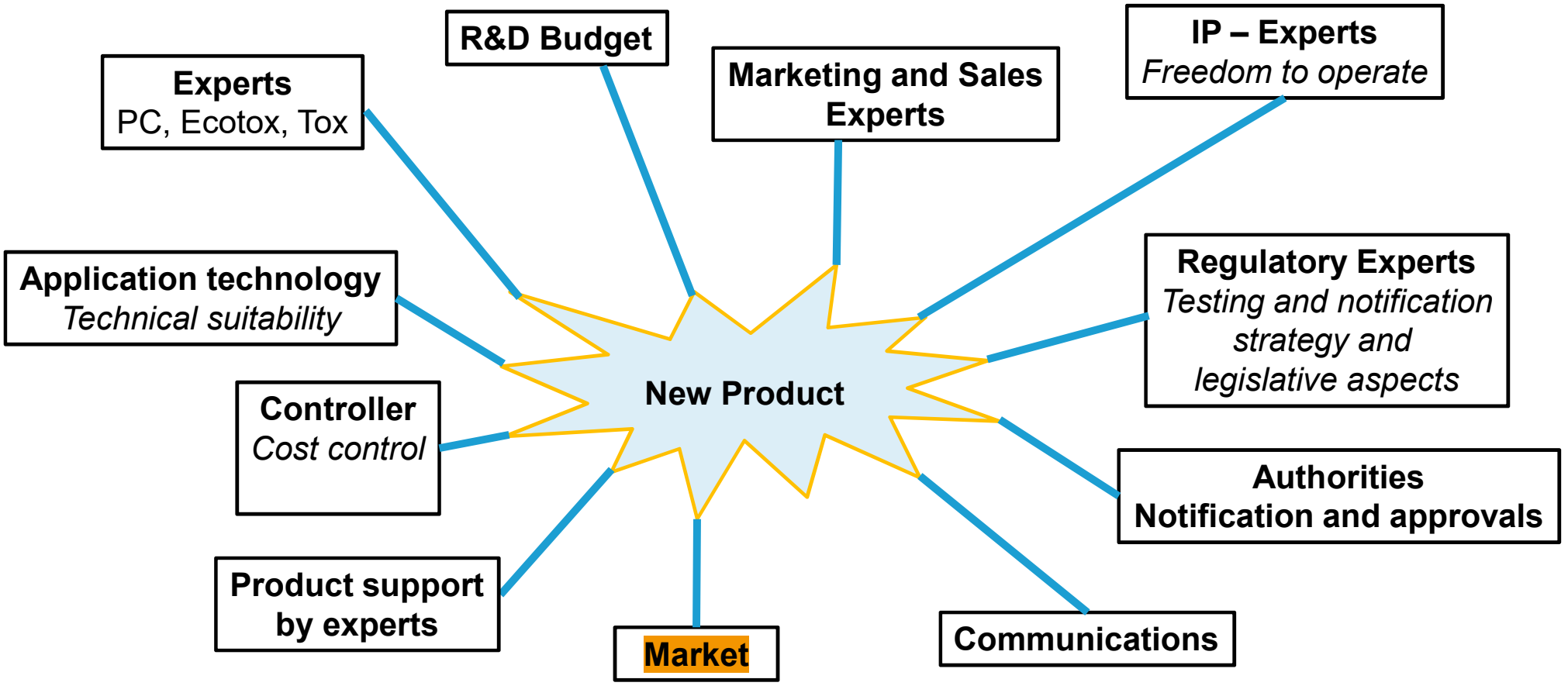
Weichmacher im Spielzeug gefährden die Gesundheit von Kindern. Das weiß die Europäische Union seit Jahren. Doch die Industrie stemmt sich erfolgreich gegen Europas erstes Produktverbot. Am Montag vertagten sich die EU-Beamten erneut.
Szenen eines Lobbykrieges / Von Christian Wernicke

Nuckeln, Lutschen, Beissen. Alles, was Spaß macht, kann gefährlich werden

Flexible PVC Toys - Plasticisers under Scrutiny

- Public perception: "***Plasticiser***" is linked to "***Problem***" (no differentiation)
- Wide dispersive use of substances from different chemical classes as plasticizers in consumer goods
- Database for different plasticizers varies from poor to excellent
- Huge part of the soft PVC article (30-40% w/w) consists of plasticizer/s
- Plasticizers not covalently bound to PVC: leaching/migration ….
  - Mouthing of articles, e.g. toys
  - Dispute on duration of mouthing
    - Risk assessment with uncertainties
- Scaremongering by NGO's and media
  - Impact on reputation and business

Innovation Network



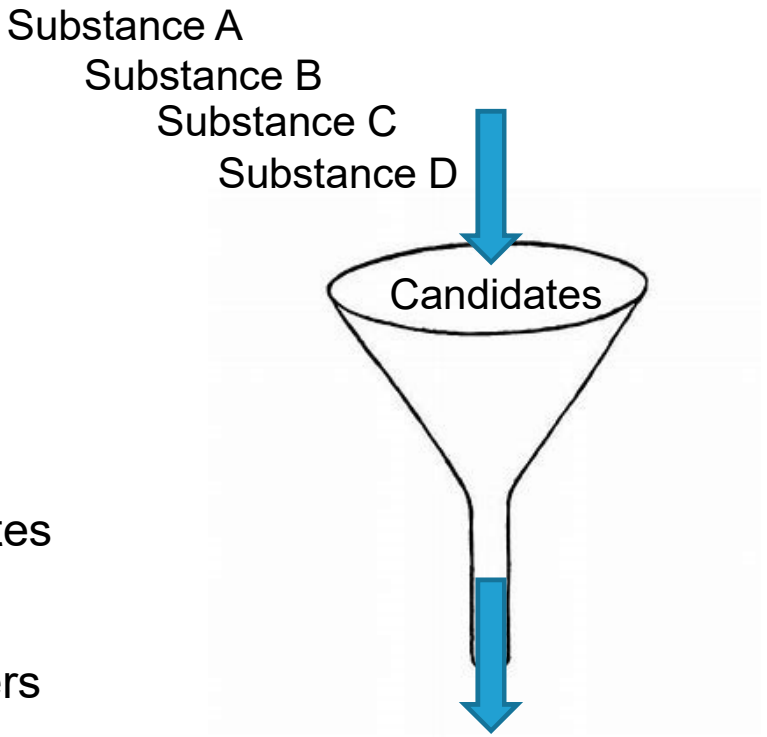
Innovation Process

- Options for innovative solutions
  - Transition from PVC to a different polymer (are all issues known?)
  - Substitution of the plasticiser

- Innovation:
  - Translation of the idea for a new plasticiser molecule into a real product for the market that provides a solution to a hitherto unsolved issue and meets regulatory and market demands
    - Suitable technical properties of the candidate molecule
    - Production
      - Raw material availability
      - Production costs
      - Production facility

Structuring the Process

- Search for candidate molecules
  - Brainstorming
  - Criteria that make a molecule eligible to be a plasticiser
- Synthesis and chemical characterization of potential candidates
- Selection and prioritization based on suitability as plasticiser
  - Application technology and involvement of target customers
- Identification of most promising candidate/s



Regulatory Testing

- Substance characterisation
  - Representative sample of the new plasticiser
- Information requirements
  - Physical-chemical properties
  - Ecotoxicological endpoints
  - Toxicological endpoints
  - Region specific chemicals legislations need to be considered
    - Adaptation of testing to meet regional requirements

REACH – Tiered Information Requirement Toxicology

Regulation (EU) 1907/2006 (REACH), Annex	VII	VIII	IX	X
t/a	≥ 1	≥ 10	≥100	≥ 1000
Skin irritation or corrosion (in vitro)	x	x	x	x
Eye irritation (in vitro)	x	x	x	x
Skin sensitization (LLNA)	x	x	x	x
Bacterial gene mutation (Ames)	x	x	x	x
Acute oral toxicity	x	x	x	x
Skin irritation in vivo		x	x	x
Eye irritation in vivo		x	x	x
Acute toxicity 2nd route (dermal/inhalative)		x	x	x
Cytogenicity study in mammalian cells		x	x	x
In vitro gene mutation in mammalian cells (HPRT)		x	x	x
In vivo mutagenicity (if indicated)		x	x	x
Reproduction toxicity (Screening OECD 421)		x	x	x
Information on Toxicokinetics		x	x	x
Short-term repeat dose toxicity (28d)		x	x	x
Repeat dose toxicity (90d)		x	x	x
Developmental toxicity (OECD 414)			x	x
Extended One-Generation Reproductive Toxicity (OECD 443)			x	x
Long-term repeat dose toxicity (≥ 12 months)				x
Mutagenicity studies (if indicated)				x
Carcinogenicity				x

Tiered information requirements exist also for physical-chemical data and for ecotoxicology

Testing proposals, Approval by ECHA

Substitution of Low Molecular Weight Phthalates - Background

- Toxicity to reproduction of rats shown by specific substances **within the active cluster**
  - Straight carbon backbone C3 to C6 and total C ≤ 8
  - Respective monoester is the active toxicant
    - Testicular toxicity leading to impairment of fertility in the rat
    - Developmental toxicity

- Current human exposure levels of the general population are low and decreasing for the critical members of the phthalate family

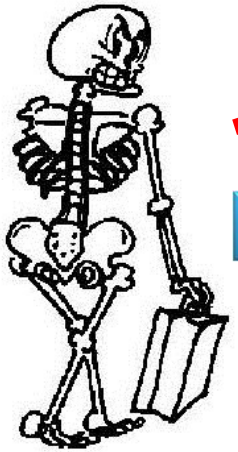
Substitution of the Plasticizer

Regulation (EU) No 1907/2006, Annex XVII, 51 and 52

Hexamoll® DINCH

Dir 67/548/EC
C3-C8
Phthalates

Toxic



Danger

Regulation (EC) No 1272/2008 (CLP)

- **New Plasticiser**
- **Other chemical class**
- **Non-hazardous (CLP)**
- **Approvals for different applications**

Challenges in the Substitution Process

- **Customers**
  - New product, not enough long-term experience
  - Your company is the only producer, there is no second supplier
  - Request to support specific applications requiring approvals (food contact, medical)

- **Competitors**
  - Not enough experience
  - Not fully tested
  - Not independently evaluated
  - Not established in the market
  - Higher price than established products

Challenges in the Substitution Process

- **NGO's**
  - New product, not enough long-term experience
  - Yet, not fully tested
    - Not a reproductive toxin, but what else?
  - All tests/studies undertaken only by the producer
  - Study details and results not available or published
  - No independent studies available
  - Not independently evaluated
  - It is just another plasticizer
  - Self-determined experts claim potential issues

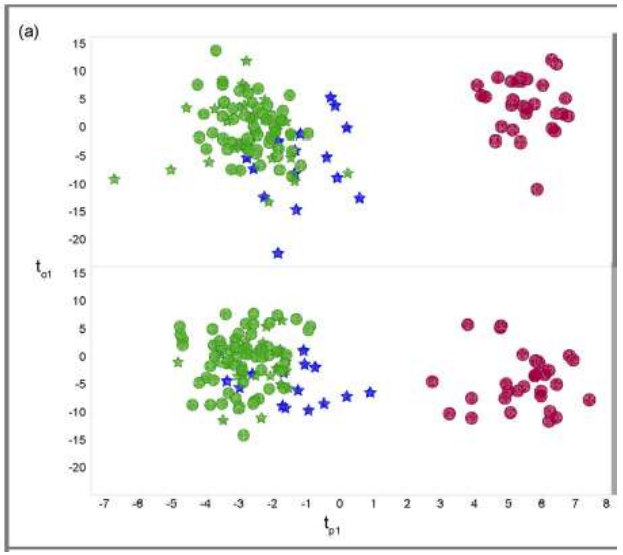
Academic Research

- Academic research depends significantly on public funding
  - Number of publications in scientific journals is used as measure of scientific productivity and impacts funding
  - Declaration “no conflict of interest” is ambiguous
  - Peer review process deteriorated
  - New business models of journals
    - Page fee model
    - Pre-peer review online publication
    - Payed, non-peer reviewed publications
    - Predator journals as an emerging topic related to junk science
- Emotional and non-targeted “**my science ⇔ your science**” discussion

	Industry/CRO Study	**Academic Study**
Guideline	Yes	No
GLP	Yes	No
Good Scientific Practice	Yes	Variable
Qualified Staff	Yes	Variable
Historical Control Data	Yes	No
Regulatory Expericence	Yes	No
Alleged Conflict of Interest	Yes	No

Unfounded Allegations against Substitutes

- Research groups from McGill University provided a series of flawed publications [Campioli 2015, Boisvert 2016, Nardelli 2017, Albert 2017, etc.]
- Claims: “Lack of published data for DINCH” and “may cause obesity, but more data needed…”
  - Rejected as:
    - Plenty of data are publicly available
    - Competent authority assessments are available
    - No obesity observed in repeat dose toxicity studies and full 2-generation reproduction study
    - Metabolic profile of Hexamoll® DINCH close to untreated controls and different from DEHP [Langsch 2018]



Metabolic profiles of male and female animals treated with either DEHP (red), Hexamoll® DINCH (blue) or untreated controls (green)

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Evaluations by Authorities and Committees

- EFSA – food contact in Europe
- NSF - drinking water in USA
- SCENIHR/SCHEER Opinions
- Evaluation by DK EPA (Denmark)
- Evaluation by KEMI (Sweden)
- EDQM – European Pharmacopoeia
- FDA – medical devices in USA
- CFDA - medical devices in China
- NICNAS – Australian competent authority (CA)
- ECHA/French CA – RMOA (Regulatory Management Option Analysis)
- German Environment Agency Germany (UBA)
  Human Biomonitoring Commission

efsa European Food Safety Authority

NSF

KEMI Swedish Chemicals Agency

edqm European Directorate for the Quality of Medicines & HealthCare | Direction européenne de la qualité du médicament & soins de santé

FDA U.S Food and Drug Administration

Scientific Committee on Health, Environmental and Emerging Risks (SCHEER)

Danish Ministry of the Environment
Environmental Protection Agency

CFDA 国家食品药品监督管理总局 China Food and Drug Administration

Australian Government
Department of Health
National Industrial Chemicals
Notification and Assessment Scheme

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Umwelt Bundesamt

Bundesministerium für Umwelt, Naturschutz, Bau und Reaktorsicherheit

Ministère de l'Écologie, du Développement durable et de l'Énergie

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Scientific Publications – Product Support for the Substitute

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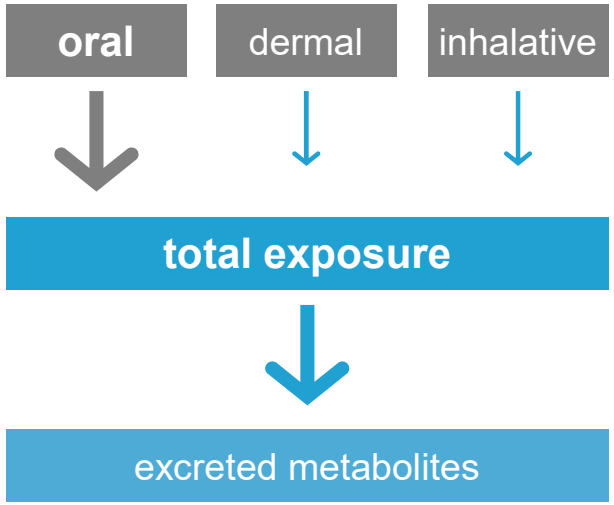
Exposure Data for High Production Volume Plasticizers

Human Biomonitoring

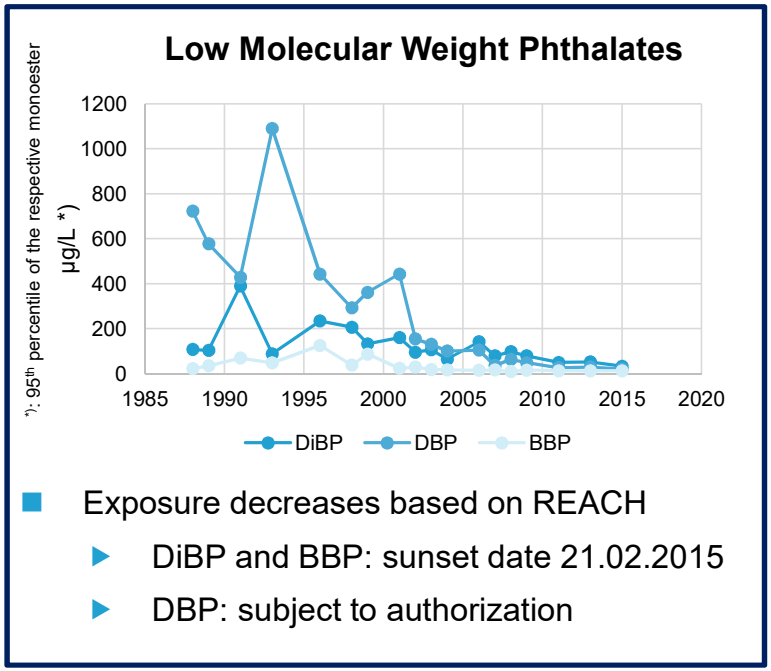
- Development of analytical methods for plasticisers
- Determination of actual human exposure
- Data substantiated risk assessment
  - Risk = Hazard x Exposure
- Independent regarding route of exposure:
  total exposure = Σ (oral + dermal + inhalative)
  - substances are not excreted as such but are metabolized
  - suitable metabolites and respective conversion factors needed



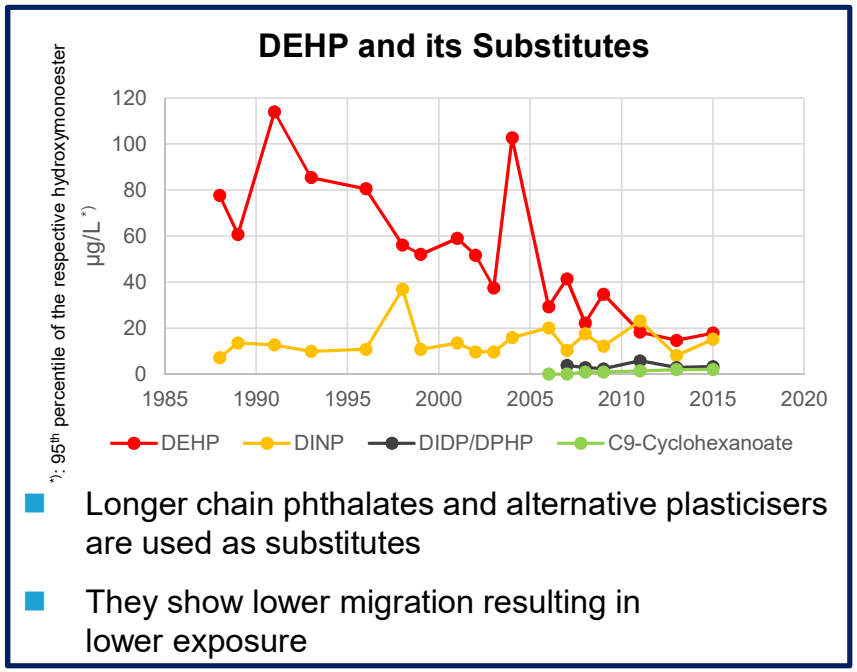
Environmental monitoring

Methods for plasticiser detection in soil, sediment, plants and air are available

Effectiveness of the Substitution Process mirrored by Exposure Trends in the General Population



- Exposure decreases based on REACH
  - DiBP and BBP: sunset date 21.02.2015
  - DBP: subject to authorization



- Longer chain phthalates and alternative plasticisers are used as substitutes
- They show lower migration resulting in lower exposure

Data source: Koch HM et al., Int J Hyg Environ Health. 2016, doi: 10.1016/j.ijheh.2016.11.003

- HBM reflects changes in use pattern based on regulatory developments and subsequent market trends
- Exposure to substitutes well below safety limits

Attacks with Unfounded Hypothetical Risks – Environmental Epidemiology and In-silico Modelling

- No need to understand the mode of action of chemicals
- No need for an animal testing facility including qualified staff
- No need for long lasting and sophisticated qualification in toxicology
- Minimal investments
  - Laptop
  - Software packages (either statistics or simple molecular modelling)
- Very efficient for quick publications with negligible scientific value
  - Letters to the editor are welcome to increase the citation index of the authors
- Basic knowledge disregarded:
  - Epidemiology is generally not suitable to prove causality
  - Computer modelling - even in color and 3D – may look nice, but needs verification by solid experimental data

Conclusion

- Innovation is vital for the chemical industry and for society
- Innovation is hard work and depends on multiple factors
- Innovation requires teamwork
- Innovation needs
  - the right people working as a team
  - the right product
  - the right time to be successful on the market
  - and „Fortune“
- Innovation is nothing you can plan – it is unpredictable
  - An inspiring atmosphere, sufficient budget and resources are essential
  - There is no guarantee for success

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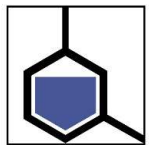

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