



Mixture effects of twenty-seven environmental contaminants given to rats at doses comparable to human exposure

Hadrup, Niels; Svingen, Terje; Egebjerg, Karen Mandrup; Pedersen, M.; Frederiksen, H.; Skov, Kasper; Frandsen, Henrik Lauritz; Vinggaard, Anne Marie

Publication date:
2015

Document Version
Publisher's PDF, also known as Version of record

[Link back to DTU Orbit](#)

Citation (APA):
Hadrup, N., Svingen, T., Egebjerg, K. M., Pedersen, M., Frederiksen, H., Skov, K., Frandsen, H. L., & Vinggaard, A. M. (2015). *Mixture effects of twenty-seven environmental contaminants given to rats at doses comparable to human exposure*. Poster session presented at 8th Copenhagen Workshop on Endocrine Disrupters, Copenhagen, Denmark.

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Mixture effects of 27 environmental contaminants given to juvenile male rats at doses comparable to human exposure

N Hadrup¹, T Svingen¹, K Mandrup¹, M Pedersen², H Frederiksen³, K Skov², HL Frandsen² and AM Vinggaard¹

¹Division of Toxicology and Risk Assessment, ²Division of Food Chemistry, National Food Institute, Technical University of Denmark, Søborg, Denmark.

³Department of Growth and Reproduction, Copenhagen University Hospital (Rigshospitalet), Copenhagen, Denmark.

Summary

Safe levels of exposure are typically estimated from single compounds without consideration of potential combination effects of several chemicals present at low levels. Here we have assessed various biological endpoints in rats having been exposed to a mixture of 27 environmental chemicals during juvenile age at levels comparable to human exposure. We found exposed rats to have compromised growth rates. Exposed animals showed no significant changes in steroid hormones, but displayed hepatotoxicity already at low level exposure. Metabolic homeostasis was also affected. We conclude that a realistic mixture of 27 chemicals, designed from knowledge on human internal exposure levels, can leave adverse footprints in young male rats.

Table: Low mix levels listed (Mid = x3; High = x10)

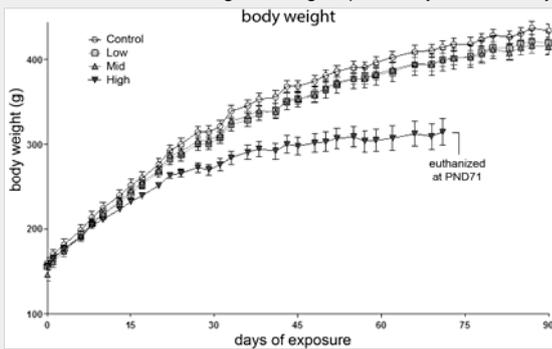
| Compound | µg/kg bw/day | Compound | µg/kg bw/day |
|-----------------------|--------------|----------------------|--------------|
| Acylamide | 4.000 | cobalt(II)chloride | 0.110 |
| Benzophenon-3 | 2.600 | leadchloride | 21.500 |
| Bisphenol A | 10.000 | mercury(II)chloride | 4.700 |
| Trichosan | 5.000 | thallium(I)chloride | 0.350 |
| o-phenylphenol | 0.060 | PFOS | 0.900 |
| trans-nonachlor | 0.350 | PFNA | 0.200 |
| p,p-DDE/4,4'-DDE | 13.000 | mono-Butyl phthalate | 62.000 |
| 2,4,6-trichlorophenol | 10.000 | AHTN | 6.200 |
| Chlorpyrifos | 0.400 | PCB 153 | 20.000 |
| 3-phenoxybenzoic acid | 0.010 | TCDD | 0.034 |
| Arsentrioxid | 3.100 | Benz[a]pyrene (PAHs) | 0.400 |
| bariumchloride,2H2O | 0.230 | PHIP | 0.100 |
| cadmiumchloride | 0.200 | MelQx | 0.050 |
| cesiumchloride | 0.610 | TOTAL | 166.104 |

LC-MS/MS analysis of several of the mixture chemicals in rat serum and urine confirmed absorption of the chemicals.

Results

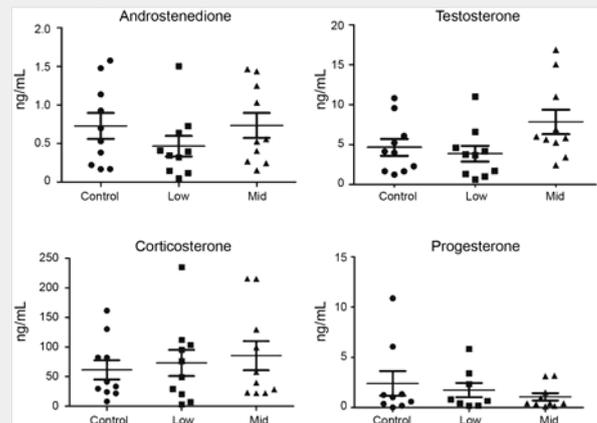
1. Mixture exposure affects growth rates

At start of exposure (6 week), all animals were comparable in size and weight. Exposed animals showed a stunted growth pattern over the 90 days, with severe effects on High-dose group already from 14 days.



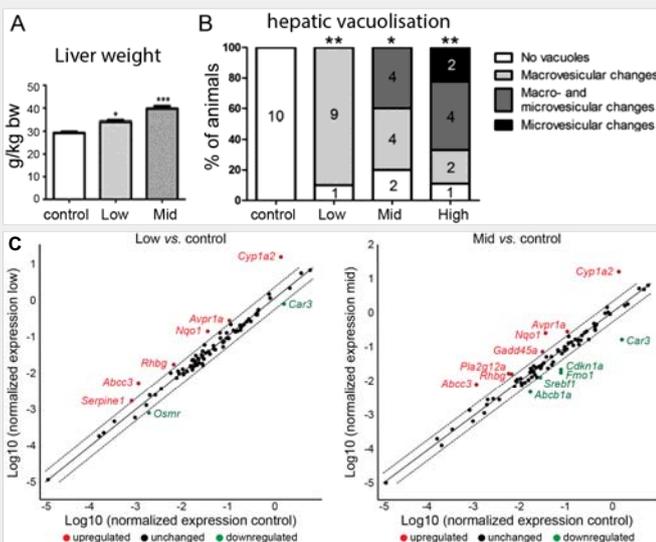
2. Mixture exposure do not adversely affect circulating steroid hormone levels

Blood serum steroid hormone levels were analysed by LC-MS/MS. No significant changes were observed between Low- and Mid-dose groups and control animals.



3. Mixture exposure causes hepatotoxicity at all doses

Following prolonged exposure, **A**) livers were significantly enlarged in the Low-dose group, with further increase in Mid-dosed animals. **B**) Hepatic vacuolisation was evident in most animals from exposed groups, with more severe pathologies in Mid- and High-dosed animals. **C**) Gene expression profiling (RT² Profiler™ PCR array) confirmed liver toxicity, with changes to transcript levels of markers for e.g. cholestasis (*Abcb1a*, *Abcc3*) and hepatotoxicity (*Cyp1a2*, *Car3*, *Fmo1*).



4. Mixture exposure disrupts metabolic/lipid homeostasis

PLS DA plots of the blood metabolome show a clear separation (HPLC-MS) of phospholipids and lipids in exposed animals relative to control. There was also a clear dose-dependent effect with a greater separation between the Mid-dose and control groups, than between Low-dose and control groups. Analyses were performed on plasma collected at 30, 60 and 90 days after initiation of dosing regimen.

