Perfluorononanoic acid in combination with 14 chemicals exerts low-dose mixture effects in rats

Humans are simultaneously exposed to several chemicals that act jointly to induce mixture effects. At doses close to or higher than no-observed adverse effect levels, chemicals usually act additively in experimental studies. However, we are lacking knowledge on the importance of exposure to complex real-world mixtures at more relevant human exposure levels.

We hypothesised that adverse mixture effects occur at doses approaching high-end human exposure levels. A mixture (Mix) of 14 chemicals at a combined dose of 2.5 mg/kg bw/day was tested in combination with perfluorononanoic acid (PFNA) at doses of 0.0125 (Low PFNA), 0.25 (Mid PFNA) and 5 (High PFNA) mg/kg bw/day by oral administration for 14 days in juvenile male rats. Indication of a toxicokinetic interaction was found, as simultaneous exposure to PFNA and the Mix caused a 2.8-fold increase in plasma PFNA concentrations at Low PFNA. An increase in testosterone and dihydrotestosterone plasma concentrations was observed for Low PFNA + Mix. This effect was considered non-monotonic, as higher doses did not cause this effect. Reduced LH plasma concentrations together with increased androgen concentrations indicate a disturbed pituitary-testis axis caused by the 15-chemical mixture. Low PFNA by itself increased the corticosterone plasma concentration, an effect which was normalised after simultaneous exposure to Mix. This combined with affected ACTH plasma concentrations and down-regulation of 11β HSD mRNA in livers indicates a disturbed pituitary-adrenal axis. In conclusion, our data suggest that mixtures of environmental chemicals at doses approaching high-end human exposure levels can cause a hormonal imbalance and disturb steroid hormones and their regulation. These effects may be non-monotonic and were observed at low doses. Whether this reflects a more general phenomenon that should be taken into consideration when predicting human mixture effects or represents a rarer phenomenon remains to be shown.

General information
Publication status: Published
Organisations: National Food Institute, Division of Toxicology and Risk Assessment, Division of Food Chemistry
Pages: 661-675
Publication date: 2016
Peer-reviewed: Yes

Publication information
Journal: Archives of Toxicology
Volume: 90
Issue number: 3
ISSN (Print): 0340-5761
Ratings:
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 4.7 SJR 1.758 SNIP 1.62
Web of Science (2016): Impact factor 5.901
Web of Science (2016): Indexed yes
Original language: English
Keywords: Mixture toxicology, Steroidogenesis, Testosterone, Corticosterone, Pituitary hormones, Perfluorononanoic acid (PFNA)
DOI:
10.1007/s00204-015-1452-6
Source: PublicationPreSubmission
Source ID: 104650189
Research output: Contribution to journal › Journal article – Annual report year: 2015 › Research › peer-review