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Federal Department of Home Affairs FDHA
Federal Food Safety and Veterinary Office FSVO
Risk Assessment Division

Bundesinstitut für Risikobewertung

Joint safety evaluation of substances in printing inks by Germany (BfR) and Switzerland (FSVO)

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6th EFSA FIP Network FCM Meeting
Parma, 10.-11.7.2018

Overview

- Joint safety evaluations by Germany and Switzerland
  - Methodology
  - Latest evaluations
- Conclusions

Cooperation between Germany and Switzerland

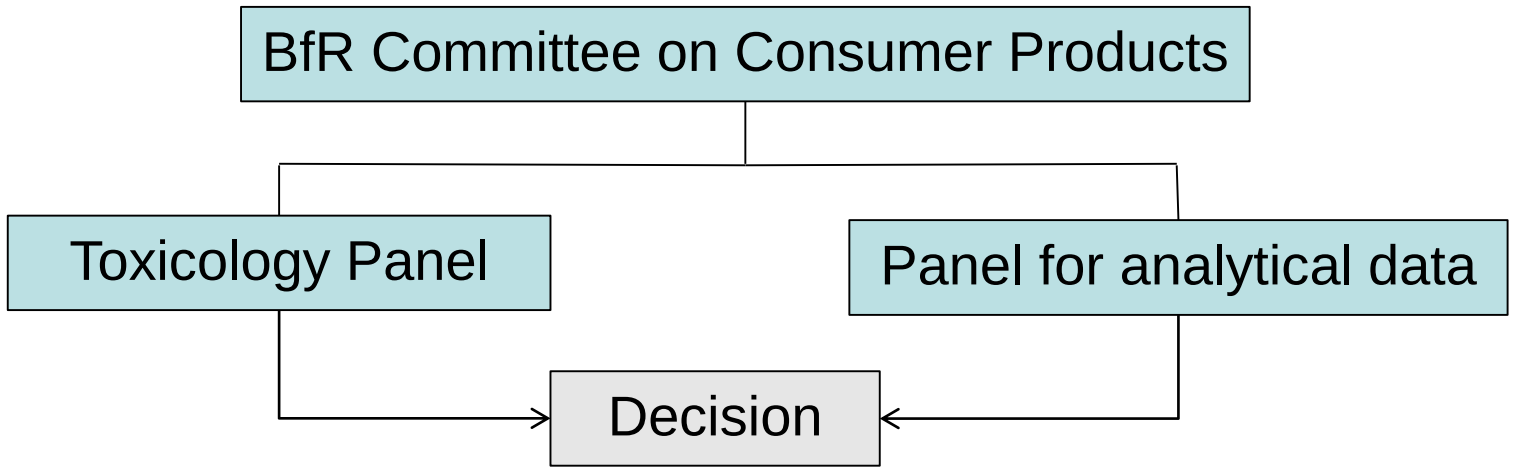
- For the evaluation of substances in printing inks, close cooperation between the Swiss FSVO with the German Federal Institute for Risk Assessment (BfR), Commission for Consumer Products, Toxicology Panel and Panel for evaluation of analytical data

- Aim: Harmonization of the authorized substances and the SML values between Switzerland and Germany (part A only)

- Harmonized procedure in the evaluation of new submitted substances between FSVO and BfR

Organisation and meetings

- Twice per year meeting, April and November at which the submitted dossiers are discussed and approved



- Sometimes, demand for supplementary data
- Evaluation by toxicologists and chemists of BfR and FSVO

Key points for joint evaluations of printing inks

- 64 petitions received since 2011
  - 29 petitions could not be finished yet
  - 6 new petitions in 2016 and 2017
- approx. 5 substances are evaluated per year
- separate evaluations are carried out by BfR and FSVO
- discussion twice a year: subgroup toxicology of commission for FCM at the BfR
- 1 evaluator for toxicology and non-toxicology each at FSVO and at the BfR

Key points for joint evaluations of printing inks

2 petitions received since 2017

- Surfactant in a water based ink:
  - intended use: indirect food contact packaging materials

- Developer for ink laser making and thermal paper
  - Intended use: indirect food contact packaging materials

List of permitted substances (Swiss Ordinance)

List	Substance category	Part A		Part B
			10/2011	
I	Monomers	345	190	1091
II	Colorants	101	6	355
III	Solvents and energy curing monomers	80	27	183
IV	Additives	705	414	2412
V	Photoinitiators	28	1	78
Sum of substances (double entries excluded) →		**1083**	**528**	**3924**

Σ = **5014 substances** (includes many monomers and additives of EU Regulation 10/2011)

Methodology for joint BfR-FSVO safety evaluations

- Data requirements for application dossiers must follow SCF guidelines:
  - characterization of substance and NIAS
  - (data on migration) / worst-case calculations
  - tiered data on toxicology
- safety assessment of substance:
  - evaluation of toxicity studies according to common practices
  - genotoxicity has to be ruled out (or genotoxic carcinogenicity)
  - MoS between lowest NOAEL and exposure estimate (migration into food; consumption of 1 kg food / person day) has to be sufficient
- safety assessment of NIAS:
  - usually migration < 50 ppb → genotoxicity could be of concern
  - different methodology can be applied: read-across to “lead”-substance, QSAR-predictions, hydrolysis data

Data on migration

- Worst case calculation
- Migration data from process / quality control of the manufacturer
  - Not worst case but realistic
  - No raw data (only table of data)
  - Mostly data from different sources (different companies / laboratories)
- Migration data in accordance with Note for Guidance

Printing inks vs. BfR Recommendations/EFSA

- Analytical data is usually not discussed in BfR Panel for analytical data
  - Discussion when necessary

- Analytical data for characterization of substances, impurities, decomposition and reaction products (IAS and NIAS) must be submitted in accordance to Note for Guidance

- Migration data is not necessary (at the moment) BUT then worst case calculation is used

Results of joint BfR-FSVO safety evaluations

- BfR:
  - risk assessment report on evaluated substance (not publically available)
  - letter to petitioner laying down SMLs for substance (and NIAS) and purity requirements (endorsed by the FSVO)

- FSVO:
  - risk assessment report on evaluated substance (in German, not publically available)
  - inclusion of SML and remarks (e.g. concerning purity requirements) for evaluated substance in Annex 10, part A of Swiss ordinance on FCM

Conclusions

- SCF guidelines and practices of EFSA CEF panel are followed in safety evaluations.
- The joint safety evaluation works out to be efficient and effective and to be well accepted by petitioners.
- Results of safety evaluation (SML) are published in Annex 10, part A of Swiss ordinance on FCM.

Latest evaluations since July 2017

- New evaluations discussed in November 2017:
  - **HEP** (2-Pyrrolidinone, 1-(2-hydroxyethyl) CAS 3445-11-2)
  - **Dynol TM 360** (1-octanol, reaction products with epichlorohydrin and 2-mercaptoethanol CAS 928768-73-4)
  - **MIBC** (4-Methyl-2-pentanol CAS 108-11-2)

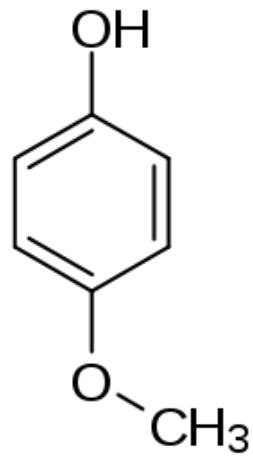
- New evaluations discussed in April 2018:
  - **SABoTBA** (CAS 22450-96-0, Tri-n-butylammonium borodisalicylate)
  - **Nonylphenol** (CAS 25154-52-3)

Analytical Challenges

- Insufficient analytical characterization of substances
- No or insufficient consideration of
  - reaction products
  - degradation products
- Migration experiments:
  - Impurities and reaction by-products are often not considered

  → Is the migration comparable?

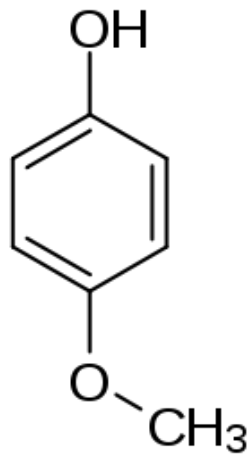
Assessment of “MEHQ” (4-Methoxyphenol)

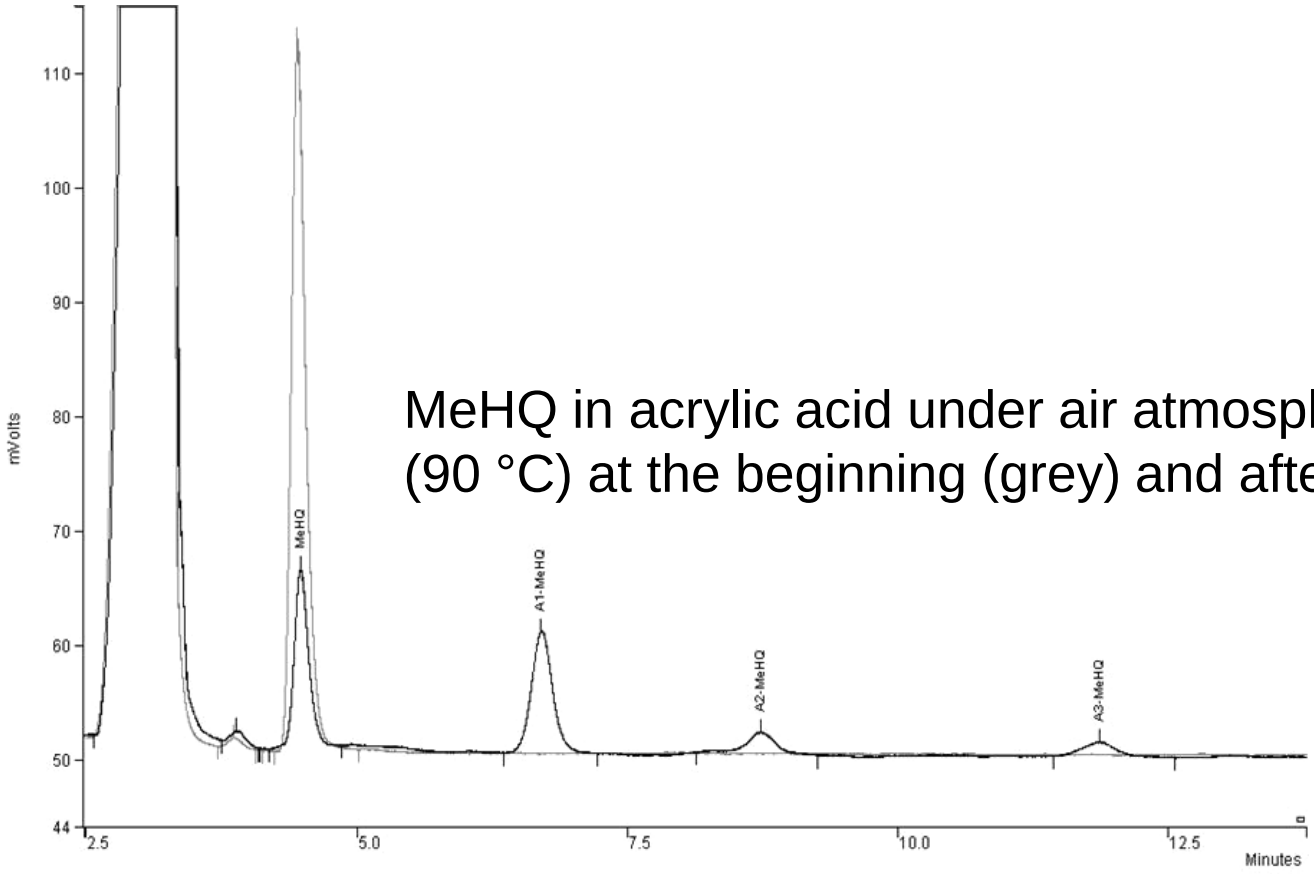


- Used as a stabilizer in the raw materials of printing inks (e. g. acrylates)
- MEHQ is a radical scavenger that inhibits polymerization in the presence of oxygen

  → prevents acrylates from polymerization
- For stabilization during storage the reaction rate is low but intentionally
  - Reaction leads to low molecular weight reaction products, otherwise the viscosity of the product would increase unacceptably

Assessment of “MEHQ” (4-Methoxyphenol)



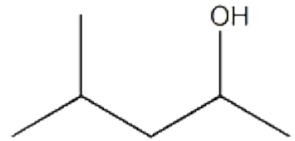


MeHQ in acrylic acid under air atmosphere
(90 °C) at the beginning (grey) and after 9 hours (black)

- Final concentration of MEHQ is low due to intentional degradation
  → Degradation products have to be considered

H. Becker and H. Vogel, *Chem. Eng. Technol.* **2006**, *29*, No. 10, 1227–1231

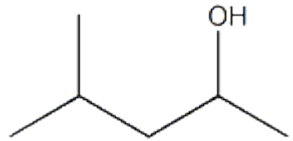
Assessment of “MIBC” – Available data



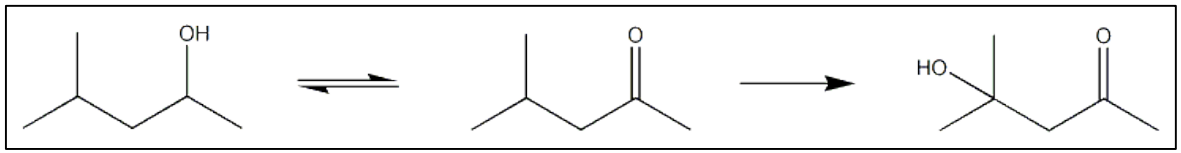
Tox data:

- MIBC: Ames test, gene mutation in mammalian cells, in vitro mammalian chromosome aberration test, toxicokinetics of MIBC and its metabolites, subacute inhalation study in rats
- MIBK: Ames test, gene mutation in mammalian cells, in vivo micronucleus test, subchronic inhalation study in rats and mice, chronic inhalation study in rats and mice, two-generation reproduction inhalation toxicity, prenatal development inhalation toxicity
- HMP: Ames test, gene mutation in mammalian cells, in vitro mammalian chromosome aberration test

Assessment of “MIBC” – Toxicology



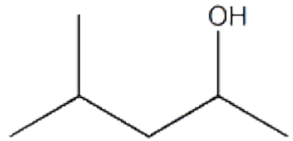
- **Toxicology:**
  - Toxicokinetics: MIBC is readily orally available. Rapid metabolization to MIBK and HMP. No indications for accumulation.



  - Lowest NOAEL from subacute study in rats: <u>43.4 mg/kg bw/day</u> (MIBC)
  - No indications for reproduction or developmental toxicity (MIBK)
  - Renal tumors in rats and liver tumors in mice with MIBK → relevance for human risk assessment cannot be ruled out: <u>LOAEL of 379 mg/kg bw/day</u> (MIBK)
  - according to IARC MIBK is: *«possibly carcinogenic to humans (Group 2B)»*

    → **genotoxic carcinogen?**

Assessment of “MIBC” – Toxicology



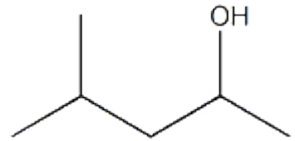
- **Toxicology:**
  - Ames tests for MIBC, MIBK and HMP negative
  - gene mutation in mammalian cells negative for MIBC, equivocal for MIBK and positive for HMP
  - in vitro mammalian chromosome aberration for MIBC and HMP negative (however studies not reliable)

    → **what about in vivo genotoxicity?**

  - in vivo micronucleus test with MIBK negative

    → **MIBC (and MIBK/HMP) are judged to be non-genotoxic**

Assessment of “MIBC” – Toxicology



- **Toxicology continued:**

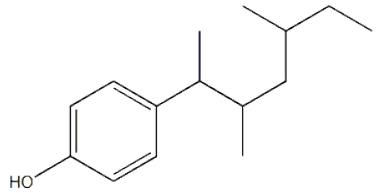
  → is a SML of 5 mg/kg acceptable?

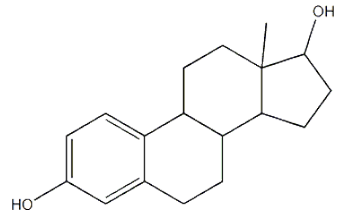
  - Exposure (EU standard cube model): 1 kg food with 5 mg/kg MIBC per day : 60 kg bw = 0.083 mg/kg bw/day
  - MoS to NOAEL of subacute study should be >500
    - MoS to $NOAEL_{subacute}$ (43.3 mg/kg bw/day):
      - 43.4 mg/kg bw/day : 0.083 mg/kg bw/day = **521**
  - MoS to LOAEL for carcinogenic effects should be > 1000
    - MoS to $LOAEL_{carcinogen}$ (379 mg/kg bw/day):
      - 379 mg/kg bw/day : 0.083 mg/kg KG/Tag = **4548**

  → MoS are sufficient.

  Thus, a SML of 5 mg/kg for MIBC (and MIBK) is acceptable.

4-Nonylphenol

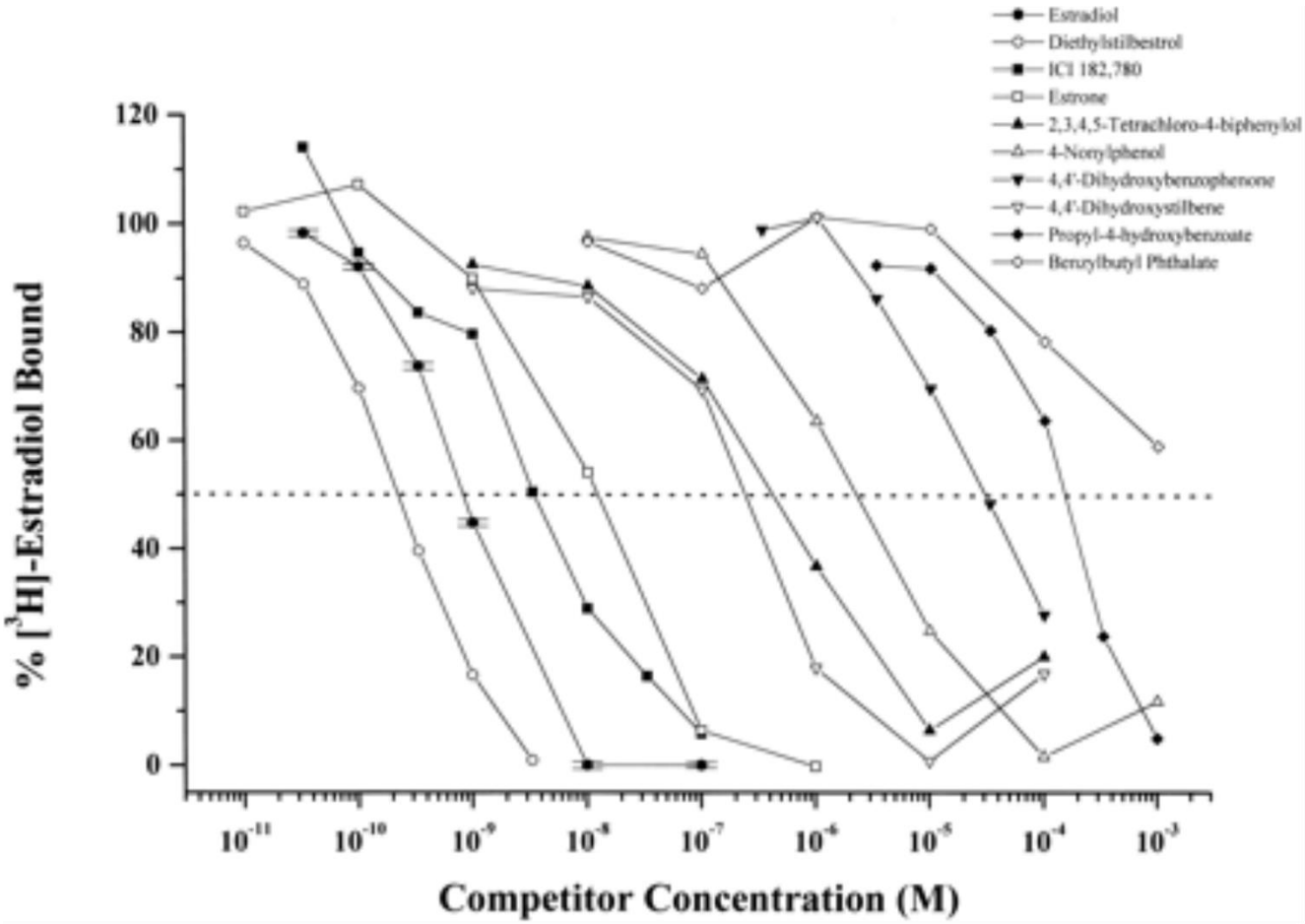




- Identified as endocrine disruptor (effects on environment)
- agonist to estrogen-receptor (alas 2-3 orders of magnitude lower binding affinity compared to 17β-estradiol; Blair et al., 2000)
- petition for use as monomer for phenolic resins
  - SML of 50 ppb → due to negative results in genotoxicity assessment this would be acceptable

- However due to caveats mentioned above a precautionary approach was chosen:

  → limit the content of free 4-nonylphenol in the resin



From: The Estrogen Receptor Relative Binding Affinities of 188 Natural and Xenochemicals: Structural Diversity of Ligands

Toxicol Sci. 2000;54(1):138-153. doi:10.1093/toxsci/54.1.138

Thank you for your attention