Multifunctional acrylate toxicology - Results of new studies generated for REACH

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Multifunctional acrylate toxicology – Results of new studies generated for REACH

- **History of toxicology testing on multifunctional acrylates**
  - Acute oral and dermal toxicity
  - Skin and eye irritation
  - Skin sensitization
  - Mutagenicity testing
  - Carcinogenicity testing
- **Some reproductive toxicology screening studies conducted**
- **Few ecotoxicology studies for aquatic toxicity conducted**

Multifunctional acrylate toxicology – Results of new studies generated for REACH

- **Results of past toxicology testing on multifunctional acrylates**
  - Acrylates generally found to be low in acute oral and dermal toxicity
  - Acrylates generally found to be eye and skin irritants, with the degree of irritation ranging from mild to severe
  - Most acrylates found to be skin sensitizers
  - Mutagenicity testing with acrylates mixed
    - **Acrylates generally found to be non-mutagenic in the Ames test (bacteria) and *in vivo* studies (studies in animals)**
  - Reproductive effects generally only seen at doses which were toxic to the mother

Multifunctional acrylate toxicology – Results of new studies generated for REACH

- **Results of past toxicology testing on multifunctional acrylates**
  - **Early dermal carcinogenicity studies at ulcerating doses found mixed results**
    - Some acrylates were found to be dermal carcinogens
    - US EPA issued a generic Significant New Use Rule (SNUR) for acrylates
      - Special labeling, precautionary measures and protective equipment
  - **Other well designed carcinogenicity studies controlling dermal irritation were negative (not carcinogenic) for the representative acrylate tested**
    - Resulted in revocation of acrylate SNURs by EPA and less concern that acrylates caused dermal carcinogenicity

Multifunctional acrylate toxicology – Results of new studies generated for REACH

- **<u>Minimum</u> toxicology requirements for high volume (≥1000 tons) REACH substances**
  - Acute oral, dermal, inhalation toxicity
  - Skin and eye irritation
  - Skin sensitization
  - Mutagenicity testing
  - Repeated dose testing (28-day)
  - Reproductive/developmental toxicity testing
  - Aquatic toxicity studies
    - **Acute toxicity to fish, invertebrates, algae**
- **Additional studies may be required**

Multifunctional acrylate toxicology – Results of new studies generated for REACH

- **High volume multifunctional acrylates tested and REACH registered in 2010**
  - Hexanediol diacrylate (HDDA)
  - Dipropylene glycol diacrylate (DPGDA)
  - Tripropylene glycol diacrylate (TPGDA)
  - Pentaerythritol triacrylate and pentaerythritol tetraacrylate
  - Diglycidyl ether acrylate of Bisphenol A (BADGEDA)
  - Trimethylolpropane triacrylate (TMPTA)
  - Propoxylated glycerol triacrylate
  - Ethoxylated trimethylolpropane triacrylate

Multifunctional acrylate toxicology – Results of new studies generated for REACH

- **Results of new studies for REACH**
  - **Hexanediol diacrylate (HDDA)**
    - A combined 28-day repeated dose (oral - gavage) toxicity study with a reproduction/developmental toxicity screening test
    - 3 doses tested
    - Some liver effects and changes in blood chemistry seen in the parent animals at the highest dose
    - Reproductive and developmental effects not seen
    - No changes to the hazard classification of HDDA based on this study
  - **HDDA remains classified as an eye and skin irritant and skin sensitizer**

Multifunctional acrylate toxicology – Results of new studies generated for REACH

- **Results of new studies for REACH**
  - **Dipropylene glycol diacrylate (DPGDA)**
    - A combined 28-day repeated dose (oral - gavage) toxicity study with a reproduction/developmental toxicity screening test (on HDDA)
    - HDDA study used as “read across” data for DPGDA
    - No changes to the hazard classification of DPGDA based on this study
  - **DPGDA remains classified as a severe eye irritant/eye corrosive, skin irritant and skin sensitizer**

Multifunctional acrylate toxicology – Results of new studies generated for REACH

- **Results of new studies for REACH**
  - **Tripropylene glycol diacrylate (TPGDA)**
    - A combined 28-day repeated dose (oral - gavage) toxicity study with a reproduction/developmental toxicity screening test (on HDDA)
    - HDDA study used as “read across” data for TPGDA
    - No changes to the hazard classification of TPGDA based on this study
  - **TPGDA remains classified as an eye, skin and respiratory tract irritant, skin sensitizer, environmental hazard**

Multifunctional acrylate toxicology – Results of new studies generated for REACH

- **Classification summary**
  - **Difunctional acrylates**

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Multifunctional acrylate toxicology – Results of new studies generated for REACH

- **Results of new studies for REACH**
  - **Pentaerythritol triacrylate and pentaerythritol tetraacrylate**
    - Registered as one substance: 2-propenoic acid, reaction products with pentaerythritol, CASRN 1245638-61-2
    - Multiple studies needed
    - Tested as a mixture (called PETIA)
    - A combined 28-day repeated dose (oral - gavage) toxicity study with a reproduction/developmental toxicity screening test
      - A number of changes in this study were attributed to the stress of the irritating properties of the test substance rather than systemic toxicity
      - No adverse reproductive/developmental effects seen
      - **No effects in this study resulted in a hazard classification change**

Multifunctional acrylate toxicology – Results of new studies generated for REACH

- **Results of new studies for REACH**
  - **Pentaerythritol triacrylate and pentaerythritol tetraacrylate**
    - Acute toxicity to fish, invertebrates (daphnia) and algae
      - **Some toxicity seen in all studies**
    - Biodegradation
      - **Not readily biodegradable**
    - Based on these studies, PETIA is newly classified as an environmental hazard
  - **Changes to the classification of PETIA**
    - Harmful if swallowed, severe eye irritant/corrosive to eyes, environmental hazard
  - **PETIA also remains classified as a skin irritant, skin sensitizer**

Multifunctional acrylate toxicology – Results of new studies generated for REACH

- **Classification summary**
  - **Pentaerythritol triacrylate and pentaerythritol tetraacrylate**

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Multifunctional acrylate toxicology – Results of new studies generated for REACH

- **Results of new studies for REACH**
  - **Diglycidyl ether acrylate of Bisphenol A (BADGEDA)**
    - Local Lymph Node Assay (LLNA) to determine skin sensitization potential - 2 studies
      - **Results: skin sensitization was seen in both studies**
    - A combined 28-day repeated dose (oral - gavage) toxicity study with a reproduction/developmental toxicity screening test
      - 3 doses tested
      - No treatment related adverse effects
      - **No changes to the classification of BADGEDA based on this study**
    - Mutagenicity
      - **2 *in vitro* (bacteria and mouse cell culture) studies not mutagenic**
      - Results consistent with *in vivo* study (mouse) conducted for the RadTech NA FCN 772 submission

Multifunctional acrylate toxicology – Results of new studies generated for REACH

- **Results of new studies for REACH**
  - **Diglycidyl ether acrylate of Bisphenol A (BADGEDA)**
    - Acute toxicity to invertebrates (daphnia) and algae
      - **No toxicity seen**
    - Biodegradation
      - **Not readily biodegradable**
    - Based on the biodegradation study, BADGEDA meets the criteria for environmental classification under the former EU Dangerous Substance Directive (DSD) but not under the current GHS CLP (Classification, Labeling and Packaging) regulation
  - **Changes to the classification of BADGEDA**
    - Skin sensitizer, environmental hazard (until CLP only)

Multifunctional acrylate toxicology – Results of new studies generated for REACH

- **Classification summary**
  - **Diglycidyl ether acrylate of Bisphenol A (BADGEDA)**

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Multifunctional acrylate toxicology – Results of new studies generated for REACH

- **Results of new studies for REACH**
  - **Trimethylolpropane triacrylate (TMPTA)**
    - A combined 28-day repeated dose (oral - gavage) toxicity study with a reproduction/developmental toxicity screening test (on HDDA)
    - HDDA study used as “read across” data for TMPTA
    - Additional older dermal studies also available
    - No changes to the hazard classification of TMPTA based on any of these studies
  - **TMPTA remains classified as an eye and skin irritant and skin sensitizer**

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Multifunctional acrylate toxicology – Results of new studies generated for REACH

- **Results of new studies for REACH**
  - **Propoxylated glycerol triacrylate (GPTA)(1- 6 moles PO)**
    - Local Lymph Node Assay (LLNA) to determine skin sensitization potential
      - **Results: skin sensitization was seen**
    - A combined 28-day repeated dose (oral - gavage) toxicity study with a reproduction/developmental toxicity screening test (on HDDA)
    - HDDA study used as “read across” data for GPTA
    - Additional older dermal studies also available
    - No changes to the hazard classification of GPTA based on any of the repeated dose studies

Multifunctional acrylate toxicology – Results of new studies generated for REACH

- **Results of new studies for REACH**
  - **Propoxylated glycerol triacrylate (GPTA)(1- 6 moles PO)**
    - Acute toxicity to fish, invertebrates (daphnia) and algae
      - **Some toxicity seen in all studies**
    - Biodegradation
      - **Readily biodegradable**
    - Unlike PETIA, because GPTA is readily biodegradable, no environmental classification is required
  - **Changes to the classification of GPTA**
    - Skin sensitizer

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Multifunctional acrylate toxicology – Results of new studies generated for REACH

- **Results of new studies for REACH**
  - **Ethoxylated trimethylolpropane triacrylate (TMPEOTA) (1-6 moles EO)**
    - Multiple studies to determine skin sensitization potential
      - **Results: skin sensitization was seen in all studies**
    - A combined 28-day repeated dose (oral - gavage) toxicity study with a reproduction/developmental toxicity screening test (on HDDA)
    - HDDA study used as “read across” data to TMPEOTA
    - No changes to the hazard classification of TMPEOTA based on the repeated dose study

Multifunctional acrylate toxicology – Results of new studies generated for REACH

- **Results of new studies for REACH**
  - **Ethoxylated trimethylolpropane triacrylate (TMPEOTA) (1-6 moles EO)**
    - Acute toxicity to fish, invertebrates (daphnia) and algae
      - **Some toxicity seen in all studies**
    - Biodegradation
      - **Readily biodegradable**
    - Unlike PETIA, because TMPEOTA is readily biodegradable, no environmental classification is required
  - **Changes to the classification of TMPEOTA**
    - Skin sensitizer

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- **Summary**
  - New data and some existing data resulted in some changes to the classification of several multifunctional acrylates

- **Resources**
  - ECHA (European Chemical Agency) website
    - **www.echa.europa.eu**
    - **Registered substances**
  - Supplier Safety Data Sheets

National Toxicology Program 2-year cancer bioassay in Trimethylolpropane triacrylate

- In December 2011, the Department of Health and Human Services' (DHHS) National Toxicology Program (NTP) released their draft technical report regarding the toxicology and carcinogenesis studies of TMPTA
  - **The report indicated that there was *some evidence of carcinogenic activity* of TMPTA in a 2-year dermal study that was conducted in rodents**
  - One of the tumors (TVM, a type of mesothelioma) identified by NTP is notably species (rat) specific and has no relevance to humans. The second tumor (uterine stromal polyp) is benign and increasingly common in female mice. Such tumors do occur in women; however, the origin (the way these tumors develop in mice and humans) is quite different. Therefore, this finding would also have no relevance to humans. The remaining tumors [uterine stromal sarcoma and hepatic (liver) neoplasms] have been inappropriately characterized by NTP as being related to TMPTA-treatment.

National Toxicology Program 2-year cancer bioassay in Trimethylolpropane triacrylate

- ***There was no evidence of TMPTA-related dermal carcinogenesis in the NTP study***

- TMPTA showed ***no increase in skin or other cancers*** in mice in an 80-week dermal study conducted in the 1980s

- Based on the results of dermal carcinogenicity studies conducted on a "representative" acrylate and methacrylate in the late 1980s, it has been the position of the United States Environmental Protection Agency (US EPA) that ***normal human exposures to acrylates, including TMPTA, and methacrylates do not present a risk of cancer***.

National Toxicology Program 2-year cancer bioassay in Trimethylolpropane triacrylate

- RadTech North America and the Specialty Acrylates and Methacrylates (SAM) Panel found numerous weaknesses in the NTP report and conclusions
  - Both RadTech and SAM provided written and verbal testimony at a February 2012 peer review meeting
    - Standard policy for a review of the study report by an independent expert review panel
  - **Based on the testimony by RadTech and SAM, the peer review panel recommended to downgrade some of NTP conclusions**
  - Further work by RadTech and SAM continue
    - Recently submitted additional documentation regarding liver tumors seen in mice that further suggest the tumors identified in the TMPTA study were within “normal” range for these animals
    - Future: Statistical analysis, peer-reviewed publication on non-relevance of tumors, other??

National Toxicology Program 2-year cancer bioassay in Trimethylolpropane triacrylate

- Under the conditions of these 2-year dermal studies, there was ~~***some***~~ ***equivocal evidence of carcinogenic activity*** of trimethylolpropane triacrylate in male F344/N rats based on ~~increased~~ marginal incidences of malignant mesothelioma. There was ***no evidence of carcinogenic activity*** of trimethylolpropane triacrylate in female F344/N rats administered 0.3, 1.0, or 3.0 mg/kg. There was ***no evidence of carcinogenic activity*** of trimethylolpropane triacrylate in male B6C3F1/N mice administered 0.3, 1.0, or 3.0 mg/kg. There was ***some evidence of carcinogenic activity*** of trimethylolpropane triacrylate in female B6C3F1/N mice based on increased incidences of uncommon malignant hepatic neoplasms (~~hepatoblastoma and~~ hepatocholangiocarcinoma) and stromal polyp or stromal sarcoma of the uterus. The occurrence of hepatoblastoma may have been related to the chemical. Dermal application of trimethylolpropane triacrylate for 2-years resulted in increased incidences of nonneoplastic lesions in the skin of male and female rats and mice.