



BUILDING A CATEGORY FOR THE REGISTRATION OF
HIGHER METHACRYLATE ESTERS UNDER REACH

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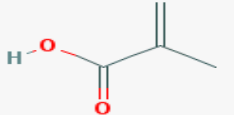
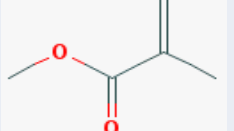
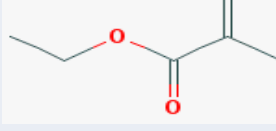
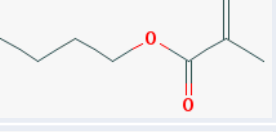
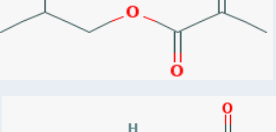

On behalf of Mitsubishi Rayon Co., Ltd
and the Higher Methacrylates REACH Task Force

Background



Lower Alky methacrylates

- Commercially important high volume chemicals
- They are related in both structure and properties
- Mammalian higher tier toxicity data sparse for all but methyl ester (MMA) and butyl ester (n-BMA)

Methacrylic acid	MAA	
Methyl methacrylate	MMA	
ethyl methacrylate	EMA	
n-butyl methacrylate	nBMA	
isobutyl methacrylate	iBMA	
2-ethylhexyl methacrylate	EHMA	

Background



- 2000/6 Category development included basic toxicokinetic studies including dermal absorption rates, ester half-life, clearance rates, etc.
- Lower Methacrylate esters were submitted as a category under OECD CICAD program
- In 2010 Registered under REACH tier 1 as single registrations & as category based upon OECD category justification
- C1-8 methacrylates of interest to OECD QSAR group
- US EPA dialog regarding experience developing categories and use in read-across

Higher Alkyl methacrylates



- The Higher Methacrylate esters are a group consisting of some 50+ chemicals
- These chemicals are of commercial interest as intermediates for the production of a wide range of polymers
- Their volume of manufacture ranges from less than 1 tpa to over 1,000 tpa
- Some are relatively data rich while others are data poor
- They are related in both structure and properties
- They lend themselves to SAR and Read-Across of data between structurally related members
- Category building offers an efficient (animal welfare) means of providing data for hazard and risk assessment purposes
- **But** data needs vary greatly and time is short (tier 2)

Category building sequence



1. Cluster esters based upon structures and properties
2. Data collection and selection of key studies
3. Identification of data gaps
4. Development of a category justification
5. Analysis of trends by end-point
6. Fitting of data with toolbox
 - Sensitivity testing with subsets
 - Broadening with other candidates
7. Identifying scientific determinant properties by endpoint
8. Proposing scientific rationale i.e. MOA
 - accounting for alerts identified for metabolites
9. Assessing data adequacy and confidence in predictions

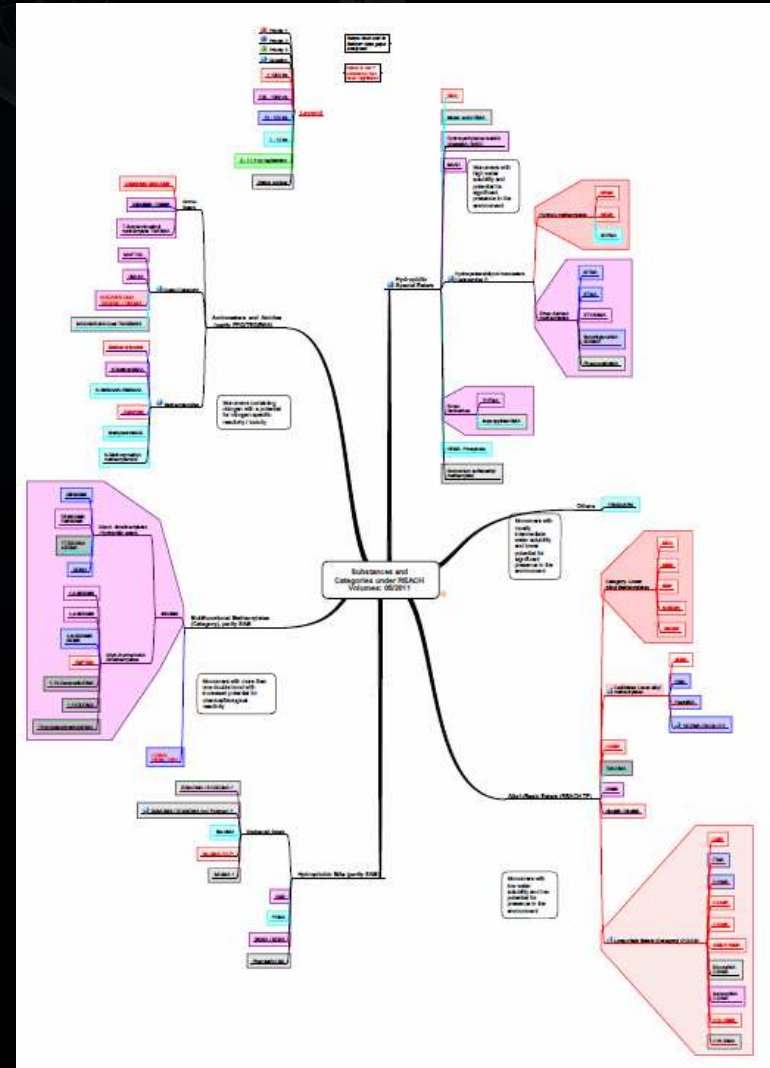
Clustering esters based upon structures and properties



Mindmaps

- Sub-groups (categories)

- Alkyl basic esters
- Hydroxy and ether esters
- Hydrophobic long chains (C12 -C22)
- Multifunctional dimethacrylates
 - Aliphatic esters
 - Glycol esters
- Methacrylamide esters



e.g. Multifunctional Methacrylates



Ester	Common Abbreviation	Structure
Triethyleneglycol dimethacrylate	TREGDMA	
Diethyleneglycol dimethacrylate	DEGDMA	
Ethylene glycol dimethacrylate	EGDMA	
Glycerol 1,3-dimethacrylate	GDMA	
1,3-Butanediol dimethacrylate	1,3-BDDMA	
1,4-Butanediol dimethacrylate	1,4-BDDMA	
1,6-Hexanediol dimethacrylate	1,6 HDDMA	
Trimethylpropane trimethacrylate	TMPTMA	

Data collection and selection of key studies



- Data collection
 - Literature searches
 - HMRTF members companies
 - SIEF
- Key study identification
- Basic data generation
 - Physical chemical properties
 - Annex 7 data

Identification of data needs



- Endpoints required for highest declared tonnage band
- Endpoints which should be waived
- Endpoints for which data or category read-across will be required
 - Endpoints required to enable interpolation (Annex 7 endpoint testing in progress)
 - Endpoints that will be read across

Development of a category justification



- Category document per sub-group
- Higher Alkyl methacrylates
- Multifunctional dimethacrylates (Aliphatic and Glycol esters) and Hydroxy and ether esters
- Populate with data specific to members
 - Structures and properties
 - Summary tables by endpoint

Category/SAR justification studies



- Route of exposure
 - Saturated VP
 - Dermal absorption evaluation
- Esters that are hydrolysed within the body
 - Basic Toxicokinetics
 - Ester half-life in vitro
 - blood and liver hepatocytes
 - K_M/V_{max}
 - Bridge to studies on lower esters
 - GSH QSAR predictions
- Relatively low toxicity but some are recognised Contact Allergens (Michael addition)
 - Contact allergy/biological reactivity battery
 - Peptide binding (DPRA)
 - Dendritic cell line activation assay MUSST
 - ARE reporter assay - LuSens

Analysis of trends by end-point



- Pin ends of category with data (interpolation)
- Description of trend(s)
- Assessment of adequacy of existing data
 - Concordance of data and anomalies
- Toolbox SAR Predictions for data gaps
- Sensitivity testing with subsets
- Broadening category with other candidates

Identifying determinant properties by endpoint



- Theorised basis for the SAR correlation observed
- Reason for outlier(s)

Proposing scientific rationale



- Mode of Action (MOA) where possible
- Accounting for alerts identified for e.g. metabolites
 - alcohol toxicity
 - Derivation of NOELS by interpolation
 - Modelling blood/ target organ tissue levels vs NOELs

Assessing data adequacy and confidence in predictions



- Established MOA or not
- Quantity and concordance of data
 - Goodness of fit
 - Residual uncertainty i.e. justification of assessment factor

Challenges



- Justifying read-across when key members are of low volume (limited data)
- What to do when half-life of parent ester is significant
 - Interpolation between reference chemicals
 - Toxicity alerts for the Alcohol
- Timetable and laboratory lead-in times
- Need to demonstrate SAR for data rich endpoints to provide confidence for other endpoints