The Impact of REACH on the Hazard Communications of US substances

Raymond M. David, Ph.D., DABT

Manager, Toxicology

BASF Corporation

BASF

The Chemical Company

Overview

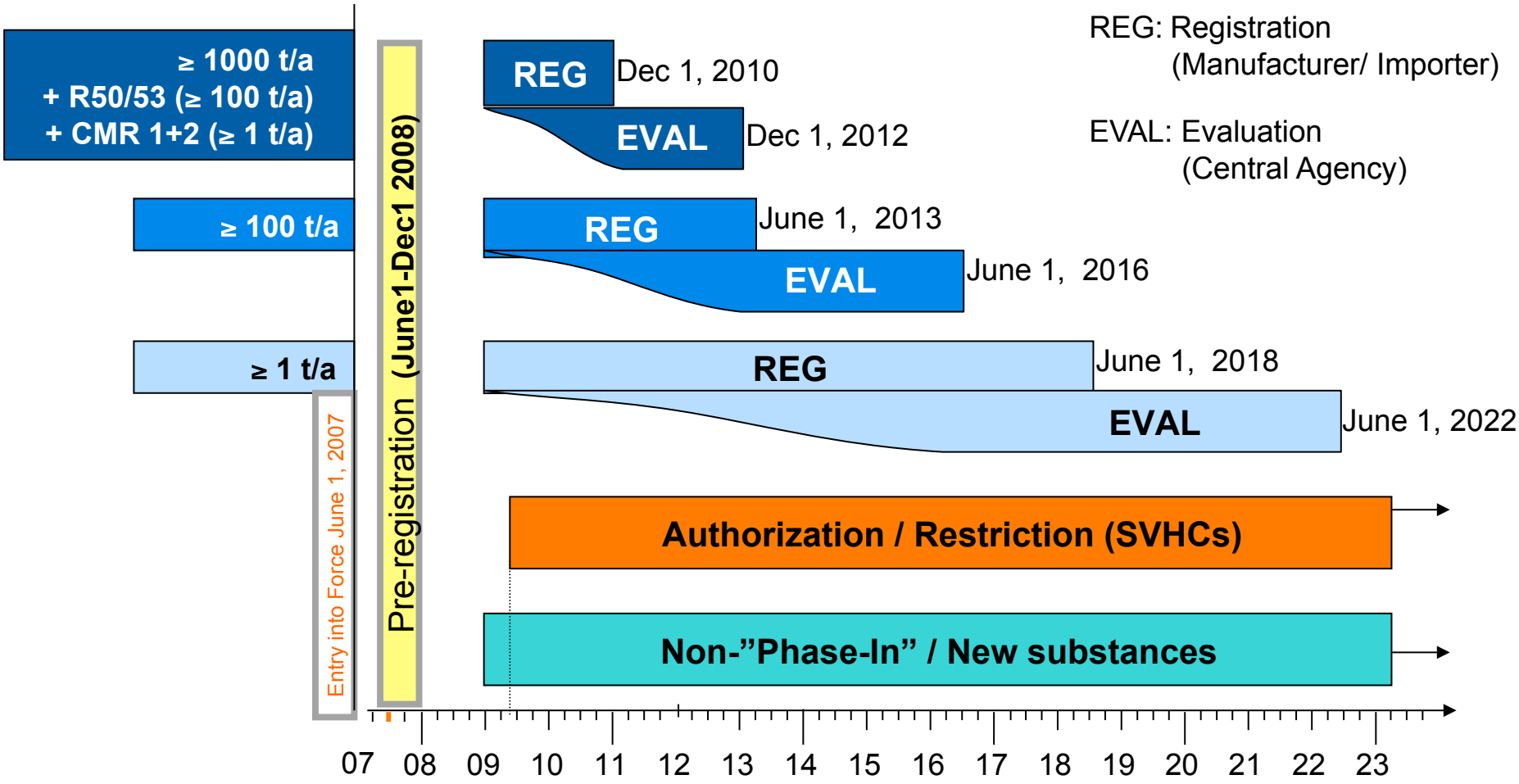
- Status of REACH registrations
  - Phase 1 substances (testing, timing)
  - Phase 2 substances (testing, timing)
- Differences in classification and labeling between old R&S, REACH/GHS
- HazComm requirements under OSHA and TSCA 8(e)
- Impact on the photoinitiators, 2-methyl-1-(4-methylthiophenyl)-2-morpholinopropan-1-one and 2-benzyl-2-(dimethylamino)-1-[4-(4-morpholinyl)phenyl]-1-butanone

Overview of EU's REACH

Registration
Evaluation and
Authorization of
Chemicals

- Main objectives
  - Consumer safety and environmental protection
  - Better knowledge and transparency about substances and uses
  - Equal treatment of new and existing substances
  - Reduce/eliminate animal testing
  - Substitution of Substances of Very High Concern (innovation driver)
  - Pay to Play (i.e. supply chain specific)

REACH timeline



SVHC = Substances of Very High Concern (CMR, PBT, vPvB, etc.)

Testing requirements

Toxicology Requirements for REACH Substance Registrations			
Volume Trigger ≥ 1 ton/a	Volume Trigger ≥ 10 tons/a	Volume Trigger ≥ 100 tons/a	Volume Trigger ≥ 1000 tons/a
1 *in vitro* Mutagenicity Test Acute Oral Toxicity *in vitro* Eye Irritation *in vitro* Skin Irritation *in vivo* Skin Sensitization	3 *in vitro* Mutagenicity Tests Acute Oral Toxicity *in vitro* Eye Irritation *in vitro* Skin Irritation *in vivo* Skin Sensitization	3 *in vitro* Mutagenicity Tests Acute Oral Toxicity *in vitro* Eye Irritation *in vitro* Skin Irritation *in vivo* Skin Sensitization	3 *in vitro* Mutagenicity Tests Acute Oral Toxicity *in vitro* Eye Irritation *in vitro* Skin Irritation *in vivo* Skin Sensitization
	in vivo Eye Irritation *in vivo* Skin Irritation Acute Inhalation Toxicity Acute Dermal Toxicity Repeated Dose Toxicity (28 Days) Reproduction/Developmental Toxicity Toxicokinetics	*in vivo* Eye Irritation *in vivo* Skin Irritation Acute Inhalation Toxicity Acute Dermal Toxicity Repeated Dose Toxicity (28 Days) Reproduction/Developmental Toxicity Toxicokinetics	*in vivo* Eye Irritation *in vivo* Skin Irritation Acute Inhalation Toxicity Acute Dermal Toxicity Repeated Dose Toxicity (28 Days) Reproduction/Developmental Toxicity Toxicokinetics
		Repeated Dose Toxicity (90 Days) 1 Teratogenicity Test Two-Generation Reproductive Toxicity	Repeated Dose Toxicity (90 Days) 2 Teratogenicity Tests Two-Generation Reproductive Toxicity
			Carcinogenicity Long-Term Toxicity

What makes REACH different?

- Data on registered substances available on ECHA (European Chemicals Agency) website
- Each registration requires a chemical safety report (CSR) including:
  - Description of use
  - Conditions of use
  - Exposure scenario
- CSR attached to Safety Data Sheet (SDS) – some SDS have grown by orders of magnitude
- CSR determines classification and labeling
- Burden is on registrant rather than government
  - Safe uses
  - Labeling

Labeling process in EU

- Classification and labeling is an interactive process with competent authorities with the company making recommendations rather than label being imposed
  - Company collects information, evaluates of the adequacy and reliability of the information, review of the information against the classification criteria, identifies potential hazard risk phrases (R-phrase), typically with consensus of all stakeholders, submits proposal to competent authority (CA)
  - CA responds with agreement or proposes different phrases based on their interpretation of the results
  - Final agreement is published in the Official Journal of the European Union. All companies are required to comply within 12 months of publication

Classification and Labeling

- Dangerous Substances Directive (67/548/EEC) combined a phrase with legislated language and a symbol that was easily recognizable

Symbol	T + (very toxic)	T (toxic)	Xn (Harmful)
Phrase wording	**R28 very toxic if swallowed** **R27 very toxic in contact with skin** **R26 very toxic by inhalation**	**R25 toxic if swallowed** **R24 toxic in contact with skin** **R23 toxic by inhalation**	**R22 Harmful if swallowed** **R21 Harmful in contact with skin** **R20 Harmful by inhalation**

Globally Harmonized System (GHS)

- Globally Harmonized System (GHS) of classification and labeling of chemicals. Adopted by the United Nations in 2002, it has been revised 4 times, and is slowly being adopted around the world
- Objectives are:
  - Enhance the protection of human health and the environment by providing an internationally comprehensible system for hazard communication
  - Provide a recognized framework for countries without an existing system
  - Reduce the need for testing and evaluation of chemicals
  - Facilitate international trade

Implementation of GHS

- Not all countries have adopted GHS. The EU originally had the Dangerous Substances Directive (DSD) which designated wording and symbols to be used on labels and safety data sheets. These were modified slightly when the EU adopted GHS

DSD	T+ R28		T R25		Xn R22		No phrase
LD_{50}	< 5	5-25	25-50	50-200	200-300	300-2000	2000-5000
GHS	Cat 1	Cat 2		Cat 3		Cat 4	Cat 5

R-phrases vs effects on development

R-phrase	Required language	Criteria
R 61	May cause harm to the unborn child	**clear results** in appropriate animal studies where effects have been observed **in the absence of signs of marked maternal toxicity**,
R 63	Possible risk of harm to the unborn child	results in appropriate animal studies which provide sufficient evidence to cause a **strong suspicion** of developmental **toxicity in the absence of signs of marked maternal toxicity**,

Taken from the Classification, Labeling and Packaging regulation (Regulation (EC) No 1272/2008) and Dangerous Substances Directive 67/548/EEC.

What is developmental toxicity?

- Types of developmental toxicity:
  - Embryotoxicity: pre-implantation loss, early resorption
  - Fetotoxicity: late resorption, decreased birth weight, decreased litter size, stillbirth
  - Terata: visceral defects, major skeletal defects, “closure” defects
  - Delay in developmental landmarks or decreased pup weights during lactation
- Maternal toxicity: e.g., decreased body weight, generally poor condition
- Developmental toxicity at dose levels that are toxic to dam are not considered to be relevant

R-phrases vs effects on fertility

R-phrase	Required language	Criteria
R 60	May impair fertility	**Substances *known* to impair fertility** in humans or to cause development toxicity in humans**; clear evidence in animal studies** of impaired fertility **in the absence of toxic effects**
R 62	Possible risk of impaired fertility	results in appropriate animal studies which provide sufficient evidence to cause a **strong suspicion** of impaired fertility **in the absence of toxic effects**

Taken from the Classification, Labeling and Packaging regulation (Regulation (EC) No 1272/2008) and Dangerous Substances Directive 67/548/EEC.

Testing of Photoinitiator 2-methyl-1-(4-methylthiophenyl)-2-morpholinopropan-1-one

- 1980's – Rats treated orally with 220 mg/kg bodyweight for 90 days or 330 mg/kg for 28 days showed evidence of peripheral nervous system damage (May be harmful if ingested)
- 2004 – Male and female rats were treated orally with 0, 40, 80, or 120 mg/kg body weight and mated. Many of the high-dose females lost their litters (May impair fertility). Developmental toxicity observed at all dose levels (May cause harm to the unborn child)

Change in classification for Photoinitiators

- The classification of 2-methyl-1-(4-methylthiophenyl)-2-morpholinopropan-1-one was changed under REACH implementation

	New classification	Former classification
DSD Directive 67/548/EEC	R60, R61, R22, R51/53	R22, R51/53
GHS (EU) Directive 1272/2008/EC	Repro 1B H360FD, Acute Tox. 4 H302, Aquatic Chronic 2 H411	Acute Tox. 4 H302, Aquatic Chronic 2 H411
GHS (KR):	Repro 1B H360FD, Acute Tox. 4 H302, Aquatic Chronic 2 H411	Acute Tox. 4 H302, Aquatic Chronic 2 H411
GHS (UN):	Repro 1B H360FD, Acute Tox. 4 H302, Aquatic Acute 2 H401, Aquatic Chronic 2 H411	Acute Tox. 4 H302, Aquatic Acute 2 H401, Aquatic Chronic 2 H411

Currently, R60 and R61 are self-classifications until published in Official EU journal.

Testing requirements

Toxicology Requirements for REACH Substance Registrations			
Volume Trigger ≥ 1 ton/a	Volume Trigger ≥ 10 tons/a	Volume Trigger ≥ 100 tons/a	Volume Trigger ≥ 1000 tons/a
1 *in vitro* Mutagenicity Test Acute Oral Toxicity *in vitro* Eye Irritation *in vitro* Skin Irritation *in vivo* Skin Sensitization	3 *in vitro* Mutagenicity Tests Acute Oral Toxicity *in vitro* Eye Irritation *in vitro* Skin Irritation *in vivo* Skin Sensitization	3 *in vitro* Mutagenicity Tests Acute Oral Toxicity *in vitro* Eye Irritation *in vitro* Skin Irritation *in vivo* Skin Sensitization	3 *in vitro* Mutagenicity Tests Acute Oral Toxicity *in vitro* Eye Irritation *in vitro* Skin Irritation *in vivo* Skin Sensitization
	in vivo Eye Irritation *in vivo* Skin Irritation Acute Inhalation Toxicity Acute Dermal Toxicity Repeated Dose Toxicity (28 Days) Reproduction/Developmental Toxicity Toxicokinetics	*in vivo* Eye Irritation *in vivo* Skin Irritation Acute Inhalation Toxicity Acute Dermal Toxicity Repeated Dose Toxicity (28 Days) Reproduction/Developmental Toxicity Toxicokinetics	*in vivo* Eye Irritation *in vivo* Skin Irritation Acute Inhalation Toxicity Acute Dermal Toxicity Repeated Dose Toxicity (28 Days) Reproduction/Developmental Toxicity Toxicokinetics
		Repeated Dose Toxicity (90 Days) 1 Teratogenicity Test Two-Generation Reproductive Toxicity	Repeated Dose Toxicity (90 Days) 2 Teratogenicity Tests Two-Generation Reproductive Toxicity
			Carcinogenicity Long-Term Toxicity

Communication requirements

- New testing triggers change in labeling in EU, which may take up to 1 year to promulgate across the industry after it is published
- In the US, Section 8(e) of the Toxic Substances Control Act (TSCA) requires U.S. chemical manufacturers, importers, processors and distributors to notify EPA within 30 calendar days of new, unpublished information on their chemicals that may lead to a conclusion of substantial risk to human health or to the environment
- The Hazard Communications Standard of the Occupational Safety and Health Administration (OSHA) requires addition of any new hazard to a MSDS with 90 days
- As a result, US MSDS may identify hazards before the European SDS does

Testing of Photoinitiator 2-benzyl-2-(dimethylamino)-1-[4-(4-morpholinyl) phenyl]-1-butanone

- 1-generation reproductive toxicity study conducted as part of REACH registration in which rats were treated orally with 0, 30, 100, or 300 mg/kg body weight over 1-generation. Results indicated no effect on fertility, but pups had lower body weight at 300 mg/kg (i.e., evidence of developmental toxicity)
- Results triggered submission of TSCA 8(e) notification to the US EPA with an additional statement on the MSDS warning of possible developmental toxicity that may be associated with general toxicity in dams (i.e., maternal toxicity)
- No classification or label is yet required in Europe

What does this mean for your operations?

- Prudent safe handling procedures should be used in the workplace
- Is the material from one supplier any more hazardous than the same substance from another supplier?
  - No! Whoever generates that data has the obligation to include the new hazard on the MSDS. Others may follow later, but in the US, there is no requirement as there is in Europe
- Is there a hazard for the downstream consumer?
  - Probably not because the initiator is used up in the curing process if handled properly

Summary

- REACH registrations for Phase 1 substances are completed and new labeling/SDS/Chemical Safety Reports are available on the ECHA website. Phase 2 substances are currently in process for testing and evaluation. This may lead to changes in EU SDS labels.
- There are differences in classification and labeling between old R&S, REACH/GHS which are now showing up on the SDS.
- New test results lead to changes in US MSDS under OSHA and trigger submission to EPA under TSCA 8(e).
- As a result, there have been changes on the US MSDS for photoinitiators, 2-methyl-1-(4-methylthiophenyl)-2-morpholinopropan-1-one and 2-benzyl-2-(dimethylamino)-1-[4-(4-morpholinyl)phenyl]-1-butanone.