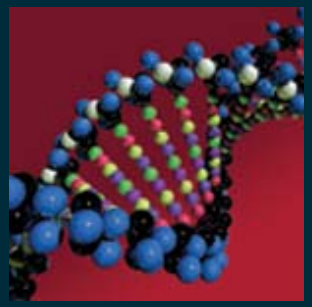
Development of the Exposure Scenario and the Role of the Industrial Hygienist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Our Discussion Points

- The REACH process
- The exposure scenario process
- Importance of the DNEL
- Derivation of the DNEL
- Comparison of DNELs and traditional occupational exposure thresholds
- Implications for the practicing industrial hygienist

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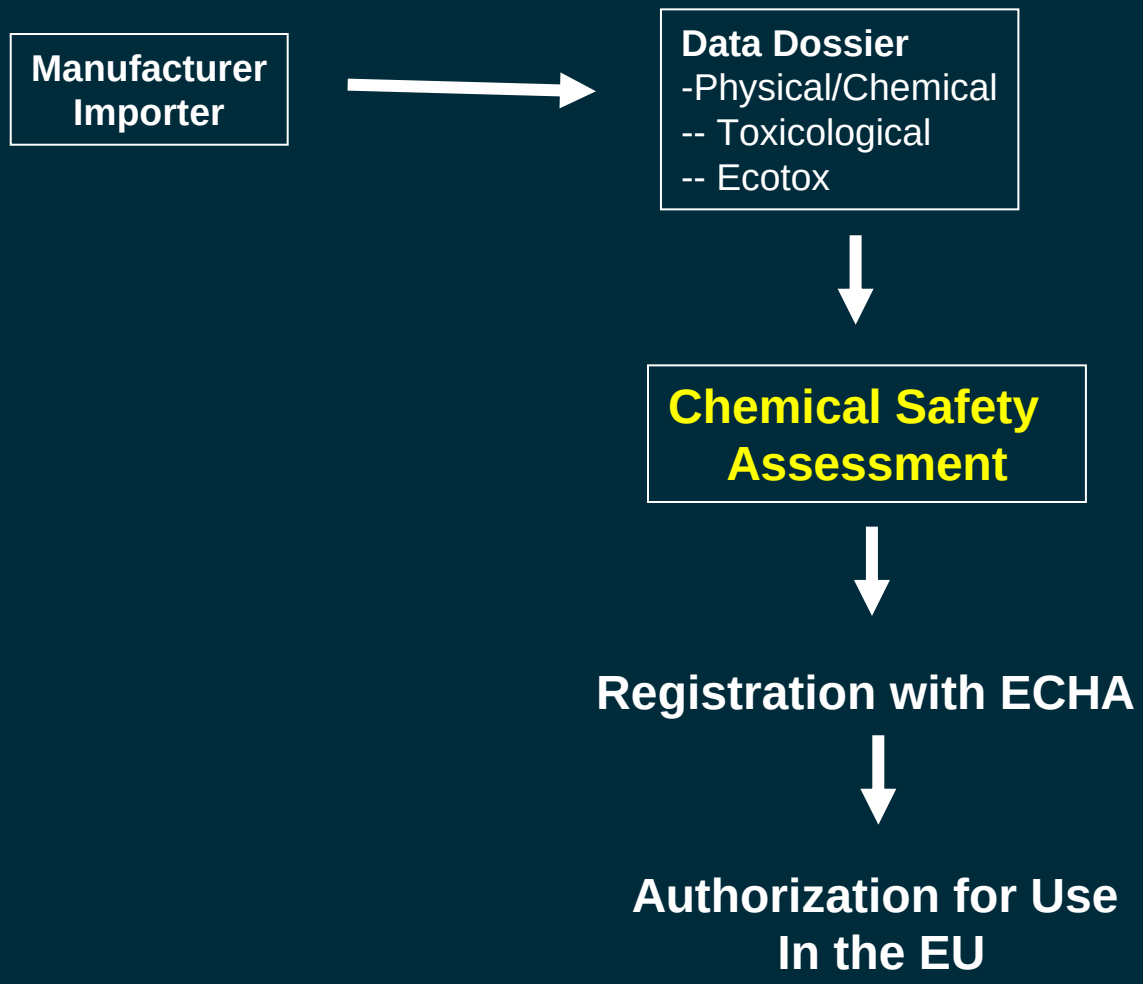
REACH Overview

- Regulation on **R**egistration, **E**valuation and **A**uthorisation and Restriction of **C**hemicals
- Passed December 18 2006, entered into force June 1, 2007
- Phased implementation over 10 years
- Estimated cost of 5 billion euro over 11 years
- References: http://ec.europa.eu, http://echa.europa.eu

REACH Registration

- Phase-in for required registrations of chemicals depending on tonnages produced or imported
- Pre-registration required for all substances manufactured or imported in quantities greater than 1 tonne/year
- Pre-registration ended November 31, 2008
- Over 130,000 substances pre-registered by over 300,000 entities
- Registration for substances required by December 12, 2010 for substances that are:
  - manufactured or imported in quantities over 1000 tonnes/year
  - Over 100 tonnes/year if very toxic to the aquatic environment
  - Over 1 tonne/year if carcinogenic, mutagenic or reprotoxic (CMR)

REACH Process



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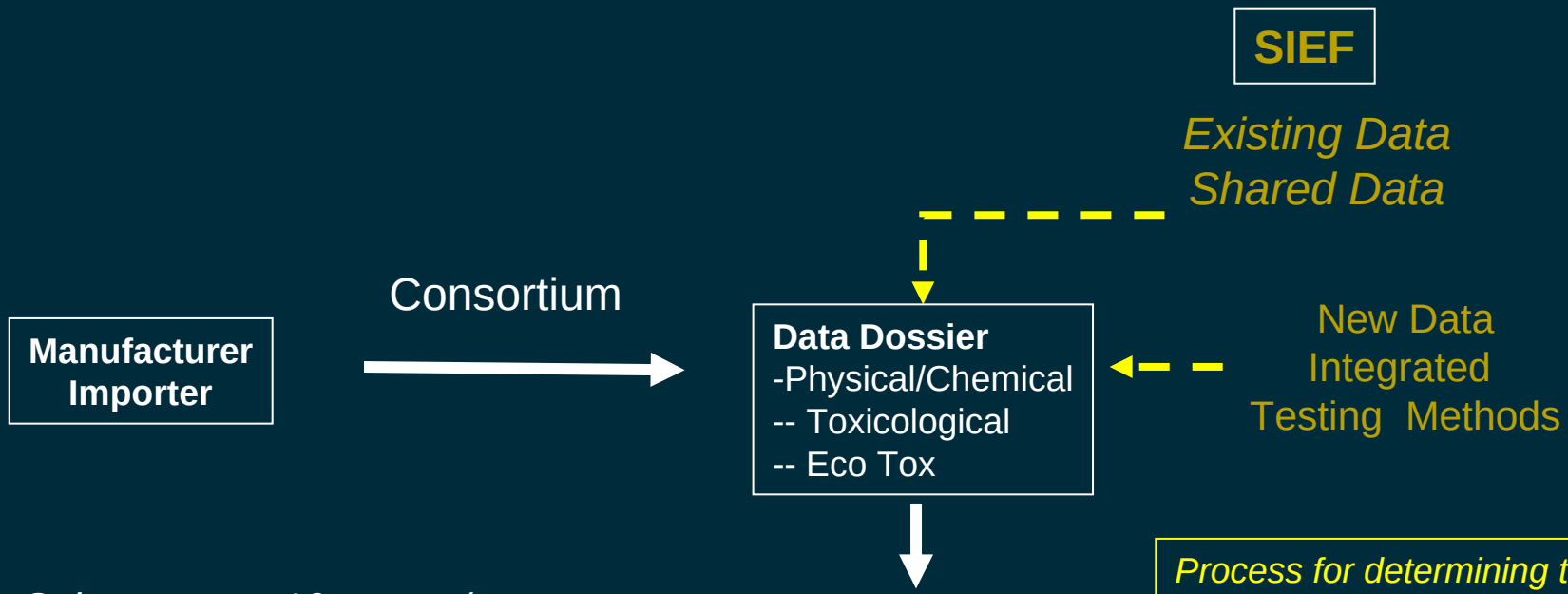
REACH Process



Substances > 10 tonnes/year
Designated "Dangerous" Substances
PBT substance
vPvB Substances

Chemical Safety Assessment

Process for determining the risk posed by a substance and, as part of the Exposure Assessment, develop Exposure Scenarios and Risk Management Measures to control risks

If substance meets criteria for classification as "dangerous" according to Directive 67/548/EEC OR has PBT/vPvB properties, Exposure Assessment and Annex I Risk Characterization are triggered

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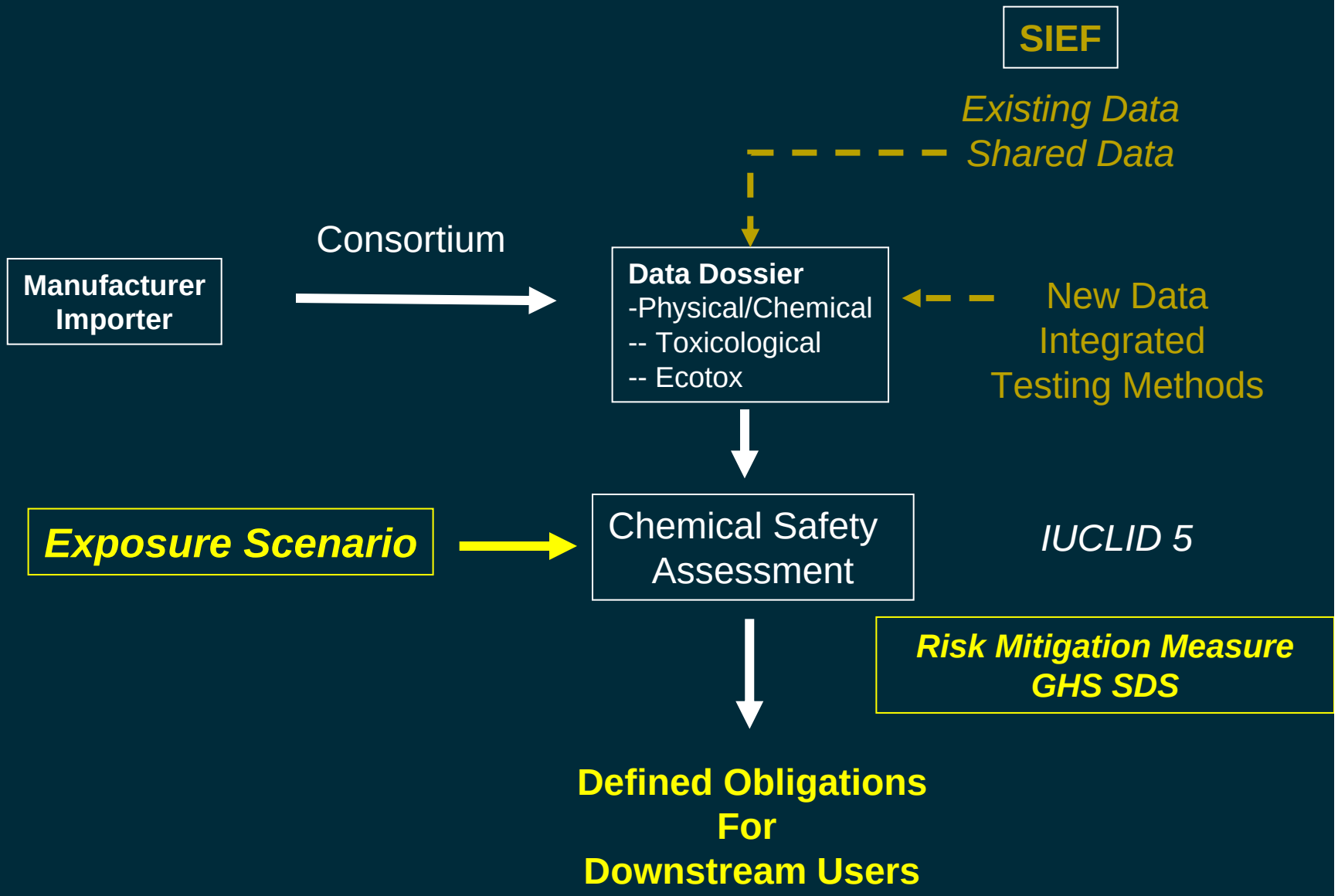
REACH Process



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The REACH Exposure Assessment

- Multiple Aspects of Exposure
  - Human Health
  - Environmental Health
  - Physical Hazards
- Through the life cycle of the substance
  - Manufacturing
  - Distribution
  - Use
  - Disposition

Collectively, the Exposure Scenario

Today we will talk about the Human Health aspects of the Exposure Assessment

Exposure Scenario

- Means the set of conditions, including operational conditions and risk management measures, that describe how the substance is manufactured or used during its life-cycle and how the manufacturer or importer controls, or recommends downstream users to control, exposures of humans and the environment.
- These exposure scenarios may cover one specific process or use or several processes or uses as appropriate

(EC No 1907/2006)

REACH Exposure Assessment Process

Exposure Scenarios

Risk Management Measures

Is Assessed Exposure Below the DNEL And PNEC?

Risk Assessment

Conditions of Use

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Exposure Assessment Overview

- Generate Exposure Scenario(s) for each life cycle stage
  - Occupational: manufacturing, formulation, professional use
  - Consumer, service life of articles, and waste
- Estimate exposure
  - based on operational conditions and risk management measures described in ES
  - Models proscribed within REACH
  - Tier 1 Models – “Reasonable Worst Case”
  - Tier 2 Models – Specific Exposure Scenario
- Characterize risk for Exposure Scenario
  - Demonstrate control of risks, safe conditions, i.e., exposure levels below DNEL or PNEC

Sources of Data and Information

- REACH Dossier Preparation
  - Existing information
  - Information from within the Consortium
  - New data
- Substance Information Exchange Forum
  - Information from third parties
- Integrated Testing Methods
  - Weight of Evidence, QSAR, read-across

Core principles for exposure estimation

- Based on sound scientific methodologies
- Describe the exposure of defined activities
- Actual exposure measurements preferred
- Collect all necessary information
- Account for RMMs in place
- External exposure

REACH Exposure Assessment Process

Exposure Scenarios

Is Assessed Exposure Below the DNEL ?

Risk Management Measures

Risk Assessment

RCR= Exposure / DNEL

RCR>1
Risks NOT Adequately Controlled

RCR<1
Risks Adequately Controlled

Conditions of Use

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What is the Derived No-Effect Level (DNEL)?

- The DNEL is the level of exposure above which humans should not be exposed
  - DNEL's intended use is in REACH risk characterization
  - Established for specific substances based on population, route of entry and duration of exposure
  - Derived for chemicals having a "threshold" mode of action
  - Potential for many different DNELs because of different combinations and exposures

Derived from typical Routes of Exposure

- Look at both Acute and Long Term Oral, Inhalation and Dermal Exposures
- Look at both Worker and General Population exposures
- DNELs may have to be established for systemic effects, local effects, or both
- Expressed as external values such as
  - mg/person-day (dermal)
  - mg/kg-day (oral)
  - mg/cm^2 body area-day (dermal); and
  - mg/m^3 (inhalation)

$$\text{DNEL} = \frac{[\text{modified}]\,\text{Dose Descriptor}}{\text{Total AF}}$$

$\text{DNEL}_{\text{(Worker-Inhalation-Long-Term)}} = \text{mg/m}^3$

4 Steps to DNEL Derivation

- Gather typical dose descriptors from all available studies on the different human health endpoints

  NOAEL; LOAEL; BMD; $BMDL_{10}$

  LD_{50}; LC_{50}; T25 (for carcinogenic response)

  Odds Ratio (OR); and Relative Risk (RR) [epidemiological descriptors]

- Decide on the substance's Mode of Action
  - Threshold MOA:

    DNEL will have to be derived for that endpoint(s) based on the most relevant dose descriptor(s) for Non-carcinogens
  - Non-Threshold MOA:

    Carcinogens

    No DNEL will be derived

    Derived Minimal Exposure Level (DMEL) will be calculated

From Robert Roy, PhD, DABT, 3M Company

4 Steps to DNEL Derivation

- Modify the relevant dose descriptors for each endpoint to the correct starting point
  - Route-to-route extrapolation of toxicity data
    - Oral → Dermal
    - Oral → Inhalation
    - Inhalation → Oral
  - Account for any differences between exposure conditions in experimental animal studies and that of the "target" human population(s)
  - Account for differences in respiratory volumes of experimental animals (rest) and humans (light activity)

Adapted from Robert Roy, PhD, DABT, 3M Company

4 Steps to DNEL Derivation

- Apply Assessment Factors (AFs) to the “modified” dose descriptor to get endpoint-specific DNEL
  - AFs used to account for the uncertainties in the extrapolation procedure and the available data set

    AFs are numerical values (defaults provided)
  - AF categories:

    Interspecies differences (allometric scaling for metabolic rate, etc.)

    Intraspecies differences (to “cover” all sub-populations such as kids, elderly, etc.)

    Differences in duration of exposure (sub-acute → subchronic → chronic)

    Dose-response issues (to get to the NOAEL)

    Quality of the entire database

Adapted from Robert Roy, PhD, DABT, 3M Company

AFs for DNELs are Proscribed by Guidance Not Determined by Scientific Consideration

Table R.8.6: Default assessment factors

Assessment factor – accounting for differences in:		Default value systemic effects	Default value local effects
Interspecies	- correction for differences in metabolic rate per body weight	AS[a, b]	–
	- remaining differences	2.5	1[f] 2.5[g]
Intraspecies	- worker	5	5
	- general population	10[c]	10[c]
Exposure duration	- subacute to sub-chronic	3	3[h]
	- sub-chronic to chronic	2	2[h]
	- subacute to chronic	6	6[h]
Dose-response	- issues related to reliability of the dose-response, incl. LOAEL/NAEL extrapolation and severity of effect	1[d]	1[d]
Quality of whole database	- issues related to completeness and consistency of the available data	1[d]	1[d]
	- issues related to reliability of the alternative data	1[e]	1[e]

[a] AS = factor for allometric scaling (see Table R.8-3)

Adapted from Robert Roy, PhD, DABT, 3M Company

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DNEL Derivation - Example

DNEL for Worker-Inhalation-Long-term-Systemic effects

- Step 1: NOAEL as Dose Descriptor
  Rat 90-day inhalation NOAEL = 350 mg/m^3 @ 6 hours/day (liver toxicity)
- Step 2: Non-carcinogenic Mode of Action
- Step 3: Modification of Dose Descriptor
  - 350 mg/m^3 x 6 hr /8 hr x 6.7 m^3/10 m^3 = 175 mg/m^3
- Step 4: Apply AFs
  - 2.5 (interspecies) [no allometric scaling needed for inhalation to inhalation]; 5 (worker; intraspecies); 2 (subchronic to chronic)
- DNEL = 175 mg/m^3 ÷ (2.5)(5)(2) = 7 mg/m^3

Adapted from Robert Roy, PhD, DABT, 3M Company

Use of the DNEL: Comparison of the Modeled Occupational Exposure

If modeled occupational exposure = 4 mg/m³

- RCR = 4 mg/m³ ÷ 7 mg/m³ = 0.6 < 1
  - "risk adequately controlled"

If modeled occupational exposure = 13 mg/m³

- RCR = 13 mg/m³ ÷ 7 mg/m³ = 1.8 > 1
  - "risk is NOT controlled"

If risk is NOT controlled → apply Risk Mitigation Measures

From Robert Roy, PhD, DABT, 3M Company

Derived DNEL Issues

- Derived DNEL
  - DNEL will almost always have to be derived for the Worker Long Term Inhalation scenario (Systemic Effects)
  - Per REACH – “Repeated Worker Inhalation for a Day or More”
- AFs are conservative in nature and proscribed
- Resulting DNELs are generally anticipated to be more conservative than other OELs

A Potential Conundrum – DNELs and other Standards

- Health-based OELs
- Indicative Occupational Exposure Values (IOELs, or IOELVs)
  - Exist for about 100 substances
- National Exposure Levels
  - Exist for about 600 substances
- Non-Regulatory Exposure Thresholds

Health-Based OELs

- Health-based OELs are prepared by a scientific committee
- The scientific community determines “overall” Safety Factor
- Consensus decision, extensive peer-review and professional comment and participation before final OEL set
- Health-based OELs have stood the “test of time”

EU IOELs

- Directives 91/322/EEC, 2000/39/EC, and 2006/15/EC
- Health-based, non-binding values
- Derived from the most recent scientific data available taking into account the availability of measurement techniques
- Set threshold levels of exposure below which no detrimental effects are expected for a given substance
- Just over 100 IOELs established
  - http://ec.europa.eu/employment_social/health_safety/docs/ioelvs_en.pdf

EU National OELs

- National OELs for 600+ substances
- Member states must take IOELs into account when they create their National OELs
  - Countries have adopted them as their National OELs
  - National OEL (from IOEL) may be higher or lower

Determining the DNEL under REACH

- May use the IOEL where one exists (with certain conditions) (Appendix R.8-13)
- May use a National OEL in lieu of developing a DNEL IF an evaluation of the scientific background for setting the national OEL is made (no further guidance given)
- If no IOEL or National OEL exist, can consider other OELs
  - ACGIH TLV®
  - AIHA WEEL
  - German MAK
  - DECOS
  - Company OEL
- Can use the information and data above but can't use the OEL values directly – Must Derive DNEL as proscribed

Issues for Consideration

- For REACH purposes...How do you derive the DNEL?
- What happens when different DNELs are derived by different registrants for the same substance?
- What happens when a non-Member State OEL, Member State OEL and DNEL for a substance are different?
- What impact does an EU DNEL have on exposure thresholds in other countries?
- How does the Industrial Hygienist utilize the information?

DNELs versus existing OELs

- DNELs will be driven primarily from worker long term inhalation exposures
- OELs, largely, are derived for a larger body of evidence
- DNELs are anticipated to be more conservative, i.e. lower, than corresponding OELs
- May in fact be significantly lower

Examples

Chemical	Health-Based OEL	EU IOEL	National OEL	DNEL	Company OEL
Chemical S	1 ppm	---	5 ppm	~ 0.1 ppm	---
A Glycol Ether	5 ppm	---	2 ppm	~ 1.6 ppm	---
Chemical C	100 ppm	200 ppm		~ 50 ppm	---
Chemical MA	200 ppm	---	200 ppm	~ 10 ppm	---
Chemical PP	50 ppm	---	20-25 ppm	~ 5 ppm	---
Chemical M	200 ppm	200 ppm	200 ppm	~ 55 ppm	

Adapted from Robert Roy, PhD, DABT, 3M Company

In Practice

- REACH DNELs are used to conduct a Safety Assessment and determine Conditions of Use for substances in certain Exposure Scenarios
  - May be existing conditions of use or may impose Risk Mitigation Measures to bring exposure below DNEL
- REACH DNELs do not displace Regulatory OELs
  - Facilities must maintain exposures below Regulatory OELs

In Practice

- DNELs may impact substance (and product) distribution and use in the EU
- These conditions of use may spill over to non-EU countries and states
- Users are still required to comply with Regulatory OELs
- Industrial Hygienists may be faced with contradictory exposure restrictions to apply in their specific situations
- There is a potential in the future for DNELs to supplant OELs, either in practice or force, but that remains to be seen

Summary

- Industrial Hygienists face some significant challenges in reconciling OELs in their regions with DNELs and conditions of use potentially proscribed in Safety Data Sheets
- Industrial Hygienists play and need to understand their significant roles in REACH
  - Development of OES(s)
  - Estimation of exposure
  - Identification of effective RMM/OC
  - Iteration of the OES(s)