EU MDR Output

Practical approaches to EU MDR Restricted Materials

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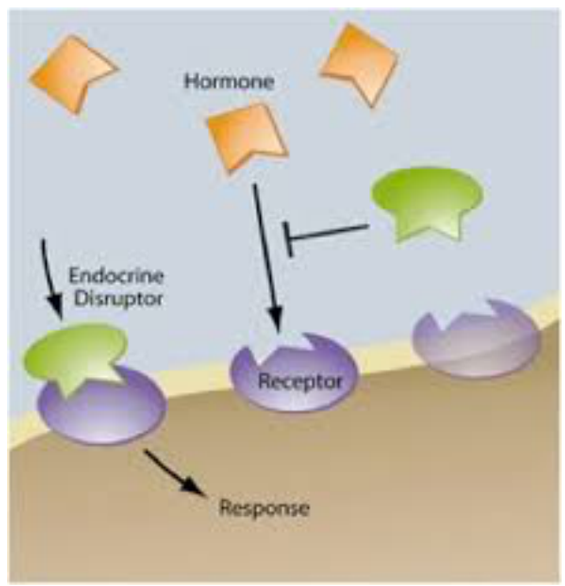
VP Consulting Services

Claigan

Overview - Agenda - EU MDR

- Introduction
- EU MDR
  - Overview
- 10.4.1
  - Degradation products
  - CMRs / EDCs
- Endocrine disruptors
- Common approaches
  - Outputs
  - Inputs
- Justification
  - New draft guidance
- Labelling
- Q&A



Webinar is 50 minutes with 10 minutes of Q&A (hopefully)

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Laboratory and Consulting Services

- EU
  - RoHS 2
  - RoHS 3 (phthalates)
  - REACH SVHC
  - REACH Restrictions
  - EU POP
  - Swedish Flame Retardant Tax
  - EU Packaging Directive
  - WEEE Directive
  - EU Medical Device Regulation
- US
  - Prop 65
  - US Toxics in Packaging
  - iMERC (Hg)
- Canada
  - Canadian Prohibition
- China
  - China RoHS
- UAE
  - UAE RoHS
- Taiwan
  - Taiwan RoHS

Claigan Environmental - Difference

- Claigan's focus
  - Compliance
  - End Deliverables

- If a step or process does not contribute to compliance or end deliverables, then it needs to be justified

EU Medical Device Regulation (EU MDR)

- Regulation (EU) 2017/745
  - EU Medical Device Regulation

- Wide range of changes and updates to medical device regulation in the EU
- Including
  - Restricted substance justification and labelling requirements

- In effect
  - May 26 2020
    - With extensions for products still under medical device directive (MDD) certificates

Historic Materials Restrictions in Medical Devices

- EU Medical Device Directive
  - No restrictions for specific substances
  - Labelling requirements for
    - Latex
    - Phthalates

- No restrictions or justification requirements

Section 10.4 Substances

- 10.4.1. Design and manufacture of devices
- 10.4.2. Justification regarding the presence of CMR and/or endocrine-disrupting substances
- 10.4.3. Guidelines on phthalates
- 10.4.4. Guidelines on other CMR and endocrine-disrupting substances
- 10.4.5. Labelling

Section 10.4.1
Design and manufacture of devices

- "Devices shall be designed and manufactured in such a way as to reduce as far as possible the risks posed by substances or particles, including wear debris, degradation products and processing residues, that may be released from the device."

- A variety of ISO standards
  - Identification and quantification of degradation products
    - ISO 10993-9:2009 - Framework
    - ISO 10993-13:2010 - Polymeric devices
    - ISO 10993-14:2001 - Ceramics
    - ISO 10993-15:2000 - Metals and alloys

Section 10.4.1
Design and manufacture of devices

- Devices, or those parts thereof, or those materials used therein that:
  - are invasive and come into direct contact with the human body,
  - (re)administer medicines, body liquids or other substances, including gases, to/from the body, or
  - transport or store such medicines, body fluids or substances, including gases, to be (re)administered to the body,
- shall only contain the following substances in a concentration that is above 0,1 % w/w <u>where justified</u>
  - Category 1 CMRs
  - Endocrine disrupting chemicals

Challenges with CMR and EDC List

- Carcinogen, Mutagen, Reproductive Toxin
  - Cat 1A and 1B
    - Roughly 2,000 substances
      - Numbers can fluctuate based on how you count substance families or overlapping EC #s

- Endocrine Disrupting Chemicals
  - Lots of competition list of potential endocrine disruptors
  - However, only official lists are
    - REACH SVHC EDCs
    - Biocide Regulation EDCs
  - Of which all currently classified EDCs are REACH SVHCs.

Endocrine Disruptors

Phthalates reproductive toxicity is from their properties as an endocrine disruptor

- *Cat 1B reproductive toxin*
- *Classified as EDC in 2017*

Two major groups of endocrine disrupting chemicals

- *Estrogenic substances*
- *Thyroid disruptors*

Endocrine Disruptors - Estrogenic

Estrogenic substances

- *Have a chemical structure similar to estrogen*
- *Triggers to the estrogen receptors to make a person or animal more female*
- *All currently classified EDCs are estrogenic*

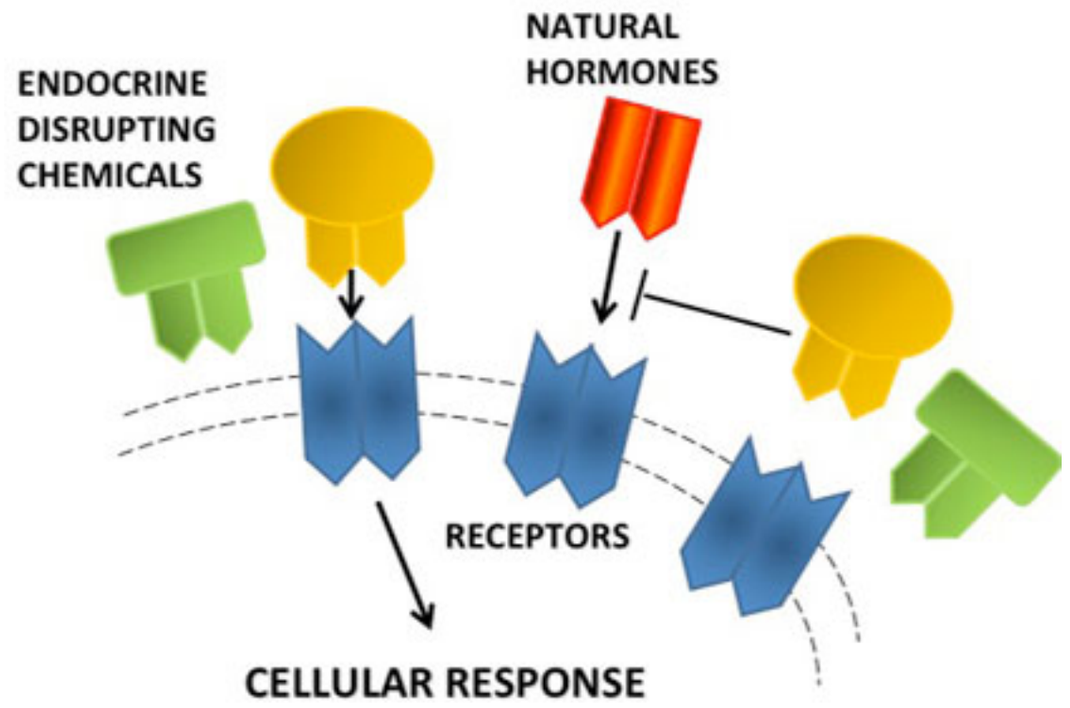
Outcomes

- *Males*
  - Attention Deficit Hyperactive Disorder
  - Low sperm count
- *Females*
  - Hyper-ovarian growth (ovarian cysts)

Endocrine Disruptors

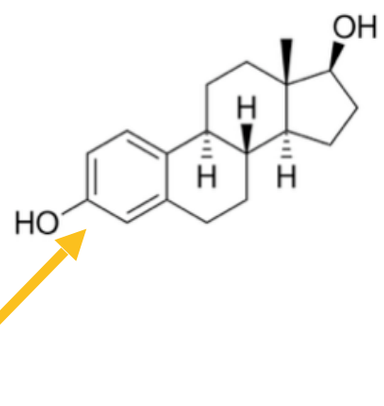
- Estrogenic EDCs
  - Keys to a lock

- Summary
  - Estradiol-like structure allows them to ‘jimmy the lock’ of the estrogen receptors



Endocrine Disruptors - Phthalate Model

Estradiol

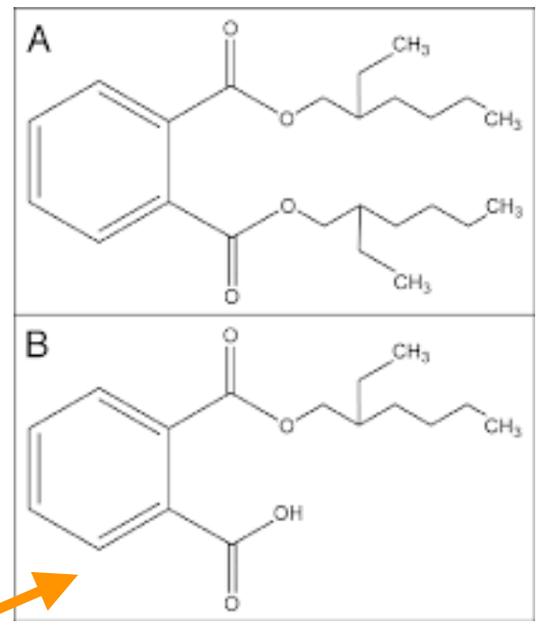


Key chemical group (phenol)

DEHP Metabolite (MEHP)

DEHP

MEHP



Estrogen-like section

Endocrine Disruptors - Estrogenic - Example Uses

Examples

Substance Group	Example	High Risk Materials
Low molecular weight orthophthalates	DEHP	PVC Polychloroprene (neoprene) Nitrile rubber Styrene butadiene rubber
Phenol ethoxylates	Octylphenol ethoxylate	Surfactant
Bisphenols	Bisphenol-A	PVC
Salicylates	Octisalate	Sunscreen
Phosphated phenols	Triphenyl phosphate	Flame retarded plastics
Benzidiols	Resorcinol	Ointments

Sources of CMR List

- No single consolidated list of EU CMRs
- CMRs applicable to medical
  - many individually or as a group have made list of CMRs and EDCs applicable to medical devices
    - Each have their usability challenges and their gaps

Common Approach to EU MDR

- Restricted Materials
  - Too many potential CMRs to test properly
  - Too few test methods for every substance

- Common plan in medical industry
  - Review of each material
  - Risk for each material
  - Action or test required
  - Result of test

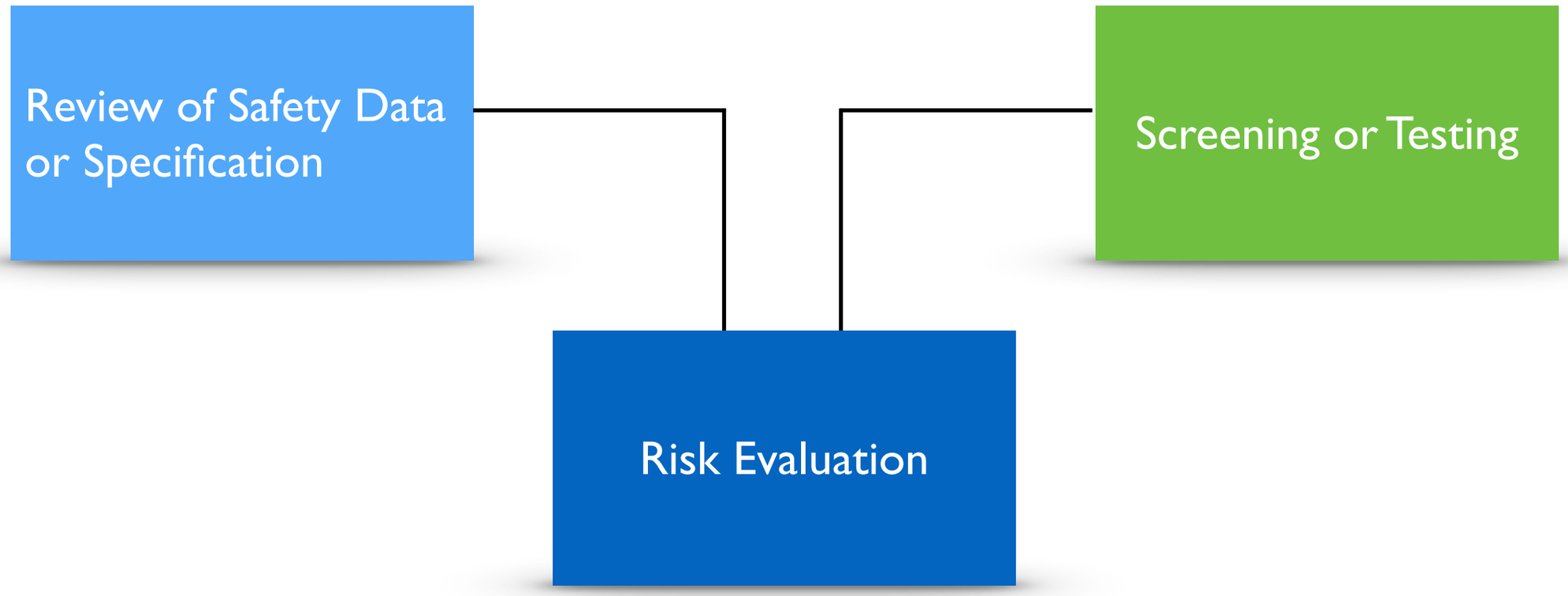
- Has to satisfy notified body

Example Output

Material		Evaluation - MDR 10.4.1		Resolution		
Type	**Locations**	**Risk**	**Comments**	**Action**	**Result**	**Document**
Polycarbonate	Housing	High	Risk of BPA	Test for BPA	Pass	BPA test result.pdf
Silicone	O-Ring	High	Sterilized by ethylene oxide	Test for ethylene oxide residue	Pass	Ethylene oxide test results A.pdf
Peek	Connector	High	Sterilized by ethylene oxide	Test for ethylene oxide residue	Pass	Ethylene oxide test results B.pdf
465 SS	Inner Tube	Low	n/a	n/a	Pass	n/a
304 SS	Outer Tube	High	Sterilized by ethylene oxide	Test for ethylene oxide residue	Pass	Ethylene oxide test results C.pdf

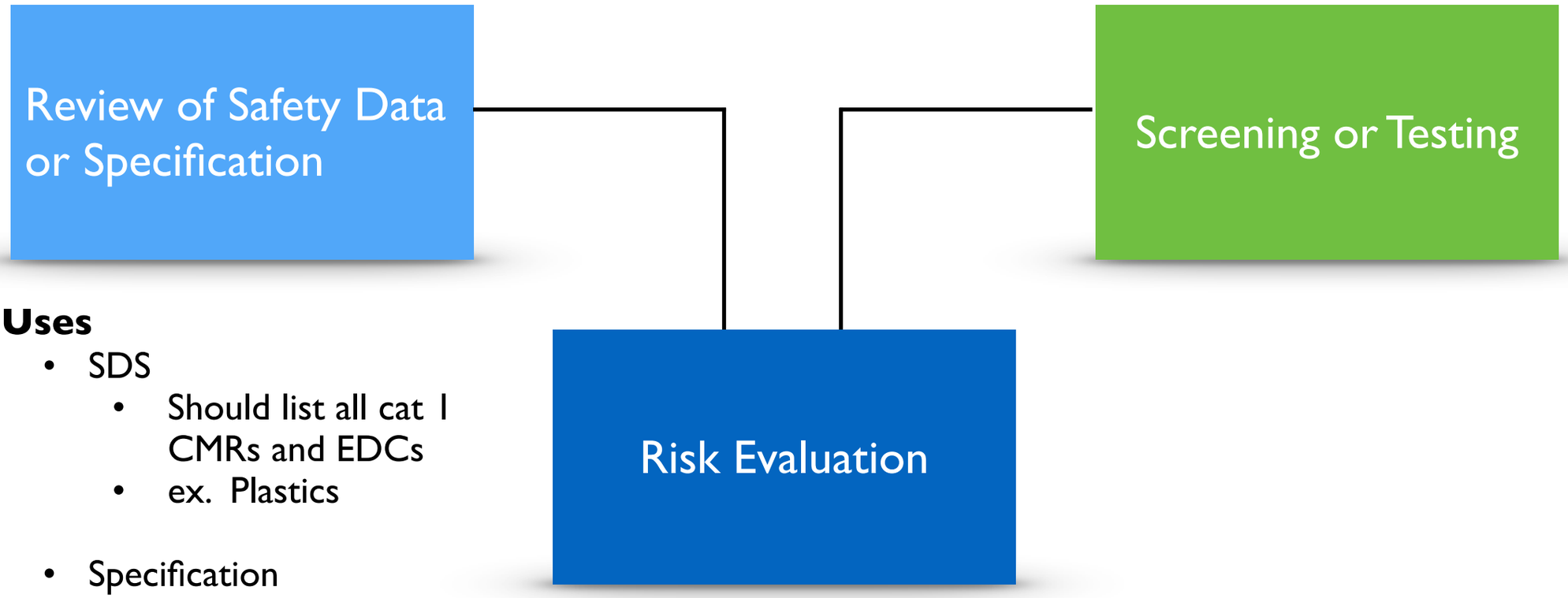
EU MDR Inputs for Risk Evaluation

- Two prong approach



EU MDR Inputs for Risk Evaluation

- Two prong approach



Uses

- SDS
  - Should list all cat 1 CMRs and EDCs
  - ex. Plastics
- Specification
  - Will often provide composition information

Gaps

- Does not normally include all materials and additives
- May not be available

EU MDR Inputs for Risk Evaluation

- Two prong approach

Review of Safety Data or Specification

Screening or Testing

Risk Evaluation

Uses

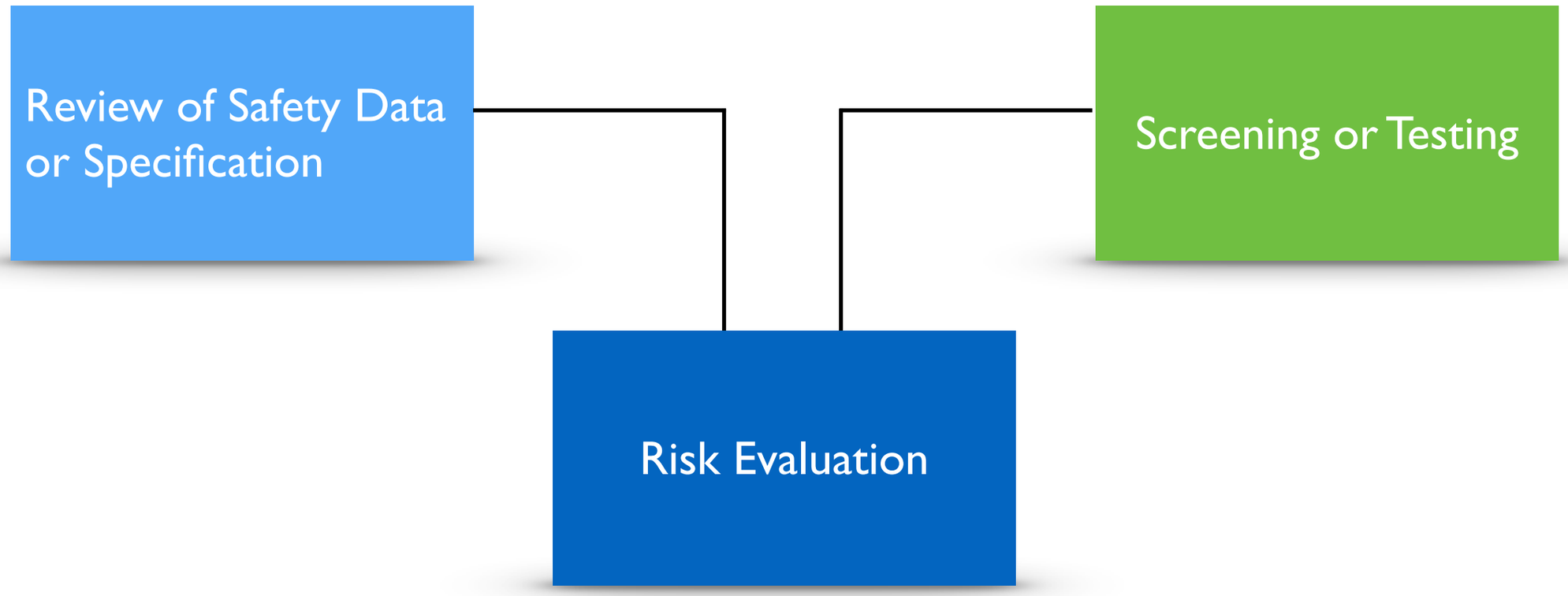
- Quantification
  - Determining concentration
- Verification
  - Verifies materials are expected materials
- Unknowns
  - Completing unknowns

Gaps

- Screening is vulnerable to missing unexpected substance uses

EU MDR Inputs for Risk Evaluation

- Two prong approach



In combination

- More complete risk assessment
- Best risk based approach

Supplier Declarations

- Not normally used as a general blanket for EU MDR compliance
  - No due diligence
  - No risk assessment
  - No standard of care

- National authorities
  - And in the case of restricted materials non-compliance, supplier documentation means nothing to national authorities unless you double checked it
    - In particular around patient safety

Definition of Invasive

- Devices, or those parts thereof, or those materials used therein that:
  - are invasive and come into direct contact with the human body,

- Question - what is the scope of invasive materials?
  - (no current guidance)

Practical Approach (Invasive)

- Practical approach
  - Include all materials in patient contact

- Why
  - Virtually all Cat 1 CMRs and all EDCs are already regulated in medical devices (REACH SVHC, RoHS, etc.)
  - (ie. you need the information anyways)
- And, if you determine a presence above 0.1% w/w, you can always re-visit the definition in detail for that specific situation

Focus back on the output

Material		Evaluation - MDR 10.4.1		Resolution		
Type	**Locations**	**Risk**	**Comments**	**Action**	**Result**	**Document**
Polycarbonate	Housing	High	Risk of BPA	Test for BPA	Pass	BPA test result.pdf
Silicone	O-Ring	High	Sterilized by ethylene oxide	Test for ethylene oxide residue	Pass	Ethylene oxide test results A.pdf
Peek	Connector	High	Sterilized by ethylene oxide	Test for ethylene oxide residue	Pass	Ethylene oxide test results B.pdf
465 SS	Inner Tube	Low	n/a	n/a	Pass	n/a
304 SS	Outer Tube	High	Sterilized by ethylene oxide	Test for ethylene oxide residue	Pass	Ethylene oxide test results C.pdf

Section 10.4.2
Justification regarding the presence of CMR / EDC

- The justification for the presence of such substances shall be based upon:
  - an analysis and estimation of potential patient or user exposure to the substance;
  - an analysis of possible alternative substances,
  - why possible substance and/ or material substitutes, or design changes, are inappropriate in relation to maintaining the functionality, performance and the benefit-risk ratios of the product;
  - the latest relevant scientific committee guidelines in accordance with Sections 10.4.3. and 10.4.4.

Section 10.4.3
Guidelines on phthalates

- By May 26 2018
  - provide the relevant scientific committee with a mandate to prepare guidelines that shall be ready before 26 May 2020
  - The mandate for the committee shall encompass at least a benefit-risk assessment of the presence of phthalates
  - The benefit-risk assessment shall take into account the intended purpose and context of the use of the device, as well as any available alternative substances and alternative materials, designs or medical treatments
  - And the benefit-risk assessment should be updated every five years.

Draft Guidelines for Phthalates

- Draft version published in March 2019

  - *Guidelines on the benefit-risk assessment of the presence of phthalates in certain medical devices covering phthalates which are carcinogenic, mutagenic, toxic to reproduction (CMR) or have endocrine-disrupting (ED) properties*

- https://ec.europa.eu/health/sites/health/files/scientific_committees/scheer/docs/scheer_o_015.pdf

Short Summary (Phthalates Draft Guidance)

- Guidelines on other CMR and endocrine-disrupting substances
  - Assessment of the presence of phthalates in a medical device
  - Assessment of possible alternative substances, materials, designs or medical treatments
  - Assessment of potential alternative substances, materials, designs or medical treatments versus phthalates
- Justification for the use of CMR/ED phthalates
- Benefit assessment

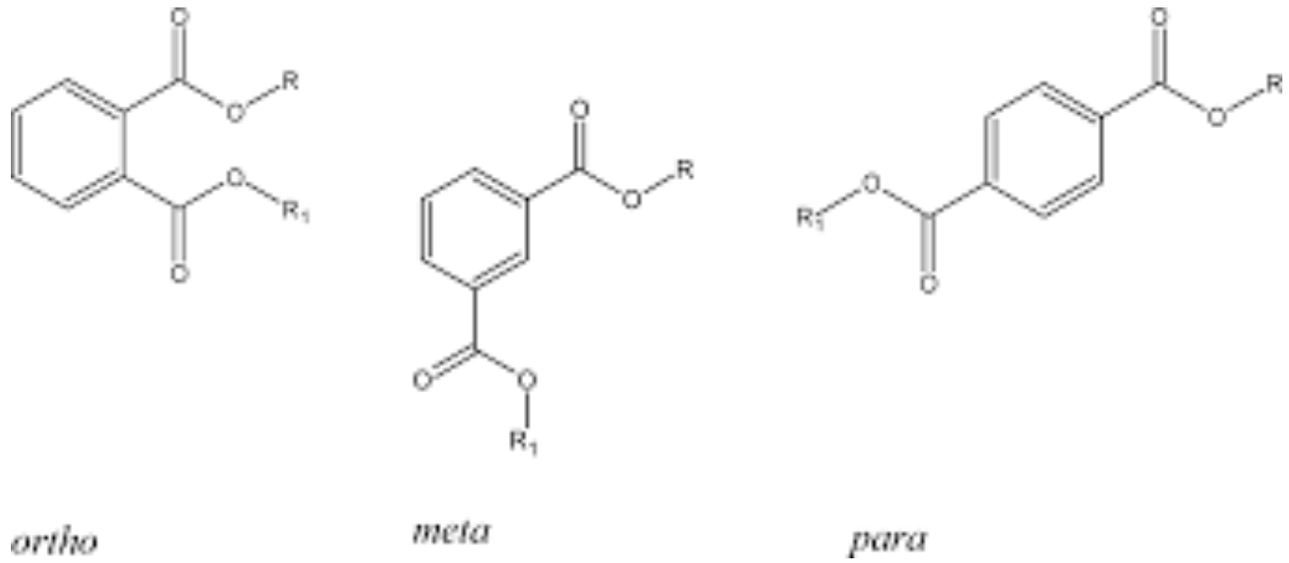
Section 10.4.2
Managing Justification in Practice

- Preferable
  - In representative simulant, Cat 1 CMR or EDCs is non detect

- Otherwise
  - Have to justify safety of Cat 1 CMR or EDC measured in simulant

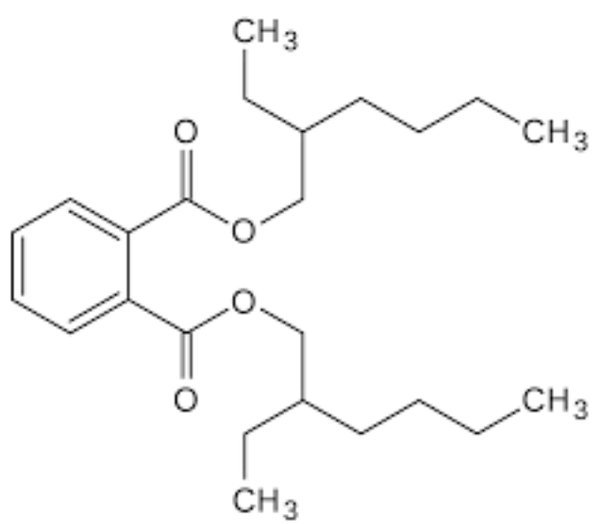
Restricted Orthophthalates

- DEHP, BBP, DBP, and DIBP are
  - Low molecular weight <u>orthophthalates</u>

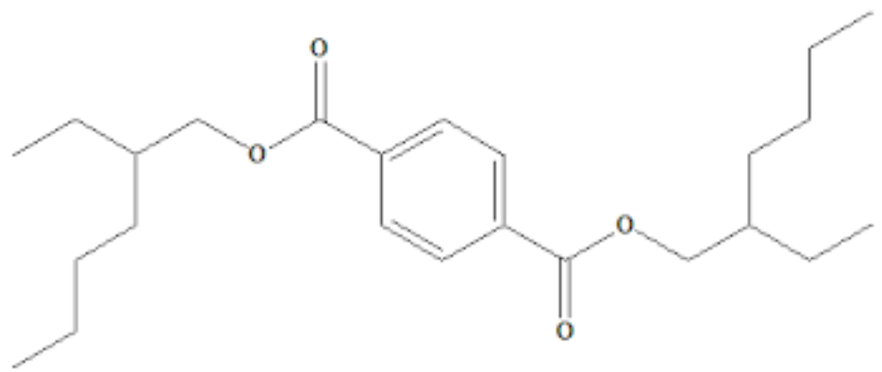


ortho *meta* *para*

Orthophthalate (DEHP)



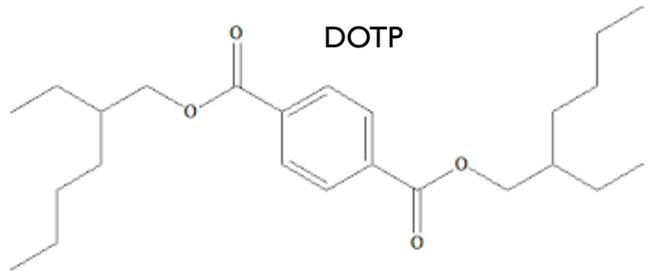
Terephtahlate (DOTP) Tere = para



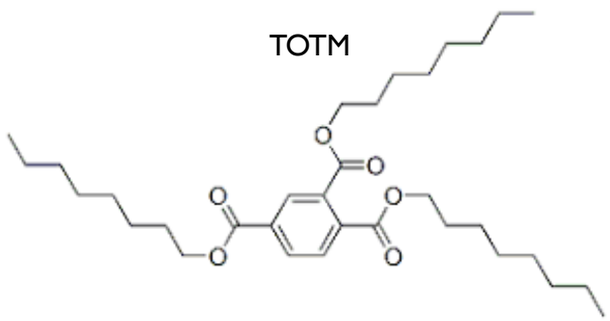
Common Orthophthalate Replacements

- Terephthalate (most common)
- Trimellitates
- Aliphatic ester
- Adipates

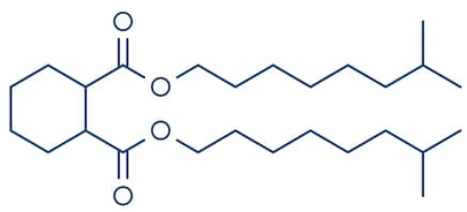
DOTP



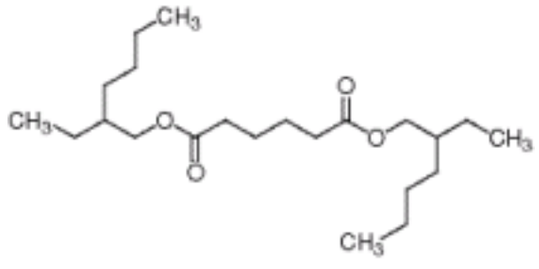
TOTM



DINCH

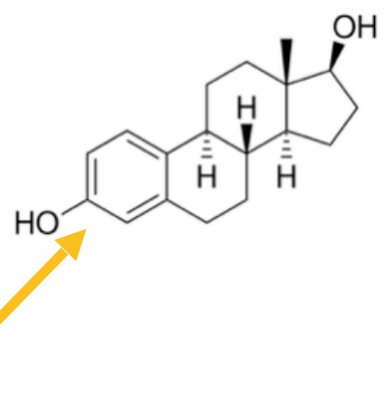


DEHA



Endocrine Disruptors - Phthalate Model

Estradiol



Key chemical group (phenol)

DEHP Metabolite (MEHP)

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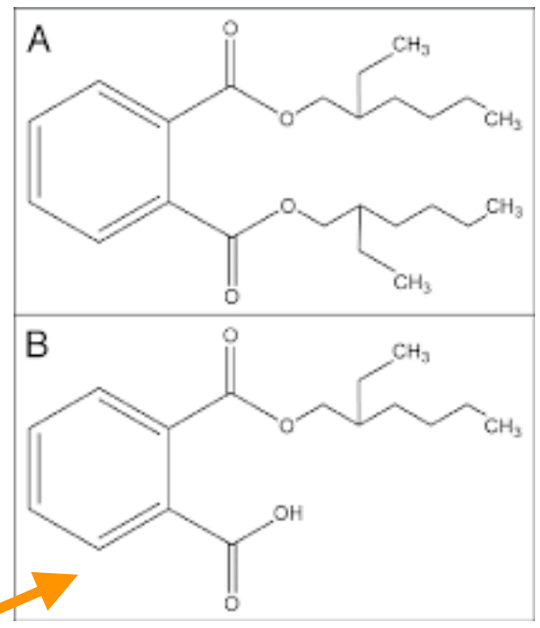

Estrogen-like section

Replacement Safety

NOAEL[1] of Ortho-Phthalate and Alternative Plasticizers

Plasticizer	Chemical Type	NOAEL, mg/kg/bw[2]	Reproductive Toxicity	Critical Endpoint
Ortho-Phthalate Plasticizers				
DEHP	Ortho-Phthalate Ester	4.8	Yes	Reproduction
DINP	Ortho-Phthalate Ester	15 (88)[3]	No / Yes[3]	Liver
Alternative Plasticizers				
TOTM	Trimellitate Ester	100	Yes	Reproduction
ATBC	Citrate Ester	100	No	Decreased body weight
DINCH	Aliphatic Diester	107	No	Kidney
DEHA	Adipate	200	Yes	Foetotoxicity
BTHC	Citrate Ester	250	No	Liver weight
DOTP	Terephthalate Ester	500-700	No	Developmental
COMGHA	Vegetable Oil-Based Ester	5000	No data	Decreased body weight

Source: EU Health & Consumer Protection Directorate-General, Scientific Committee on Emerging and Newly-Identified Health Risks

1. No Observable Adverse Effect Level. 2. Body weight. 3. Varying results of multiple studies

Phthalate Justification Going to Be Difficult

- Phthalates
  - If phthalates migrate into simulant and cause patient exposure

- Reasons justification will be difficult
  - Strong modern data on danger of phthalate metabolite
  - Replacements are readily available
  - Cost difference of replacements not significantly different
    - terepthalate, in particular, are identical price to orthophthalates
  - Safety of replacements far higher
    - In particular for vulnerable groups

Section 10.4.5
Labelling - Summary

- Requirement
  - Substances that require justification require labelling on either
    - the device,
    - the device packaging, or
    - where appropriate, on the sales packaging
      - Label
        - List of applicable cat 1 CMRs or endocrine disruptors
- Historical (EU MDD)
  - DEHP label

Section 10.4.5
Labelling - Summary part 2

- Additional requirement
  - In cases where intended use of such devices includes
    - treatment of children,
    - treatment of pregnant or breastfeeding women, or
    - treatment of other patient groups considered particularly vulnerable to such substances and/or materials
  - if applicable, appropriate precautionary measures shall be given in the instructions for use.

- This could prove challenging for reproductive toxicants and endocrine disrupting chemicals

Section 23.4
Information in the instructions for use

- The instructions for use shall contain all of the following particulars:
  - (s) information that allows the user and/or patient to be informed of any warnings, precautions, contra-indications, measures to be taken and limitations of use regarding the device.
  - That information shall, where relevant, allow the user to brief the patient about any warnings, precautions, contra-indications, measures to be taken and limitations of use regarding the device. The information shall cover, where appropriate:
  - precautions related to materials incorporated into the device that contain or consist of CMR substances or endocrine-disrupting substances, or that could result in sensitisation or an allergic reaction by the patient or user;

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Claigan EU MDR Services

- Risk assessment / testing
  - High volume lab for EU MDR restricted materials testing
    - RoHS (+phthalates), REACH SVHC, POP, Prop 65..

- Training and education
  - EU MDR Restricted Materials training
    - @Claigan, or
    - At your facility

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Q&A