# Hazard Classification Best Practices to Support a Sustainable Chemical Portfolio

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# Take Homes

- Conducting accurate hazard assessments is essential for compliance, safety, and general stewardship
- A hazard assessment you can stand by can be difficult and resource intensive
- Many resources are out there for getting toxicity information to inform assessment
- Proper documentation is key
- Toxicity information is evolving, and periodic updates are important
- New hazard classes under the European Union (EU) Classification, Labelling, and Packaging (CLP) Regulation may pose unique challenges

# Outline

- Why are hazard assessments important?
- Recap from last year
- Strategies for conducting sound hazard assessment
- Gold standard assessments
- New CLP hazard class case study

# Why Are Hazard Assessments Important?

- Compliance requirement
- Protect workers
- Needed in case of accident/spill
- Protect against litigation claims
- Know your vulnerabilities
- Build more sustainable chemical program
- Merger preparation

# Safety Data Sheets (SDSs) Not Reliable

- Often conflicting info
  - Hazards do not match toxicity data
- Lack of info
  - Hazard without toxicity data
- No hazard
  - No hazard or no data?

**Complex supply chain:**
**a SDS is only as strong as weakest link**

# Many Resources Available to Evaluate Hazard

## PubChem

- https://pubchem.ncbi.nlm.nih.gov/

## US EPA CompTox Chemicals Database

- https://comptox.epa.gov/dashboard/

## ToxPlanet

- https://www.enhesa.com/sustainablechemistry/our-solutions/toxplanet/

## ECHA Registration Dossiers

- https://echa.europa.eu/information-on-chemicals

## Agency for Toxic Substances and Disease Registry (ATSDR)

- https://www.atsdr.cdc.gov/toxprofiledocs/index.html

## US EPA Integrated Risk Information System (IRIS) Assessments

- https://www.epa.gov/iris

## US EPA Reregistration Eligibility Decision (RED) Assessments

- https://ordspub.epa.gov/ords/pesticides/f?p=chemicalsearch:1

## US EPA ECOTOX

- https://cfpub.epa.gov/ecotox/

## OECD Screening Information Data Set (SIDS) Reports

- https://hpvchemicals.oecd.org/ui/Default.aspx#Published_OECD_Assessments

## International Agency for Research on Cancer (IARC) Monographs

- https://monographs.iarc.who.int/

## National Toxicology Program (NTP) Study Reports

- https://ntp.niehs.nih.gov/publications/reports

## Joint FAO/WHO Expert Committee on Food Additives (JECFA)

- https://apps.who.int/food-additives-contaminants-jecfa-database/

## Human and Environmental Risk Assessment (HERA) Reports

- https://www.heraproject.com/RiskAssessment.cfm

## Scientific Committee on Consumer Safety (SCCS)

- https://health.ec.europa.eu/scientific-committees/scientific-committee-consumer-safety-sccs_en

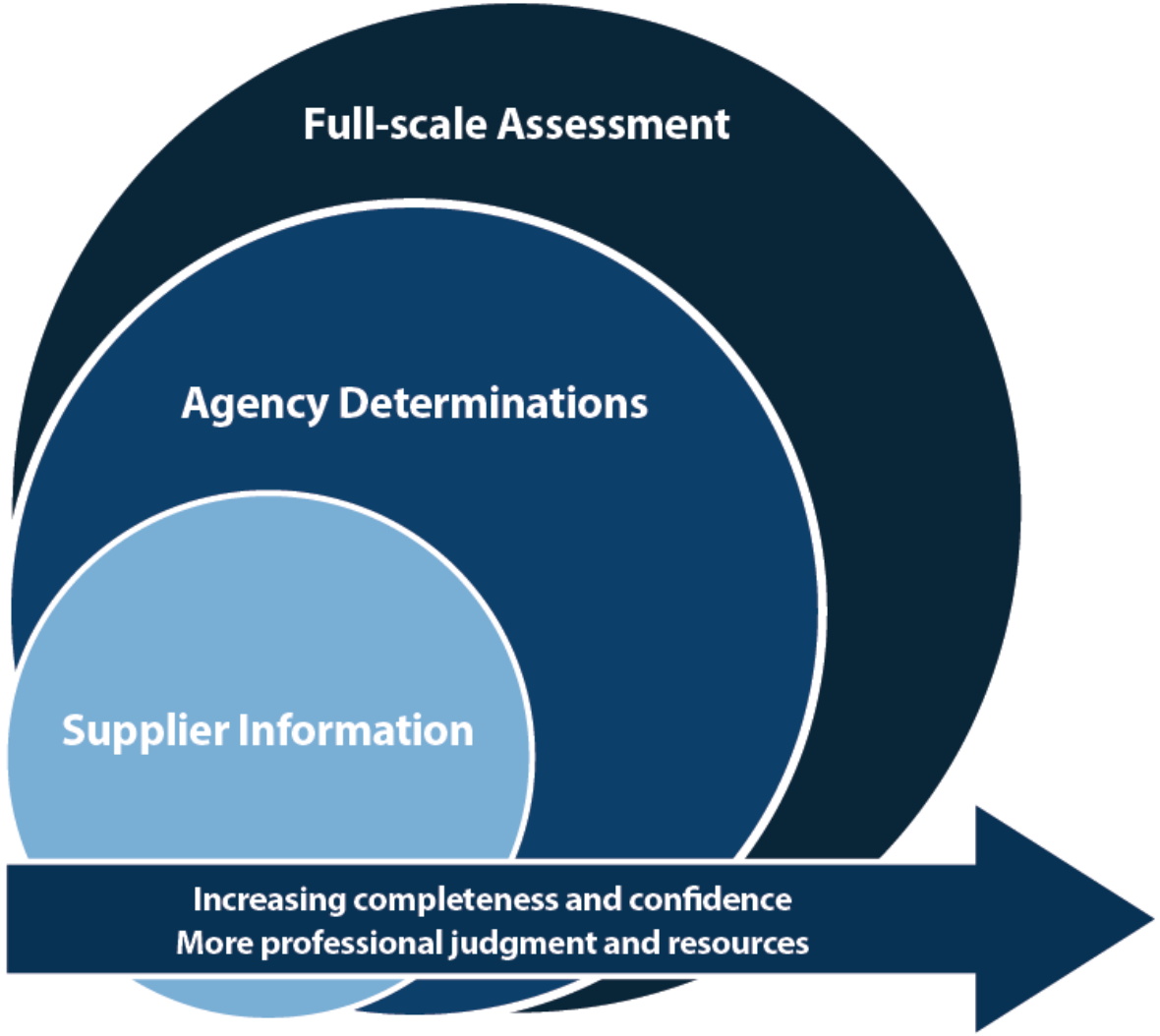
## Cosmetic Ingredient Review (CIR)

- https://www.cir-safety.org/

# Why Is Assigning Hazards So Complex?

- Supplier information may differ (rightly or "wrongly")
- Difficult to distinguish between no hazard, no data, not assessed, and assessed but unable to reach reliable conclusion
- Reliance on publicly available sources *vs.* proprietary data
- Use of read-across (surrogate)
- Authoritative hazard assignments
  - Inconsistencies among countries
  - Inconsistencies with available data
  - Differences over time
- EXPERT JUDGMENT

# Understanding Resources



# Overall Guiding Principals

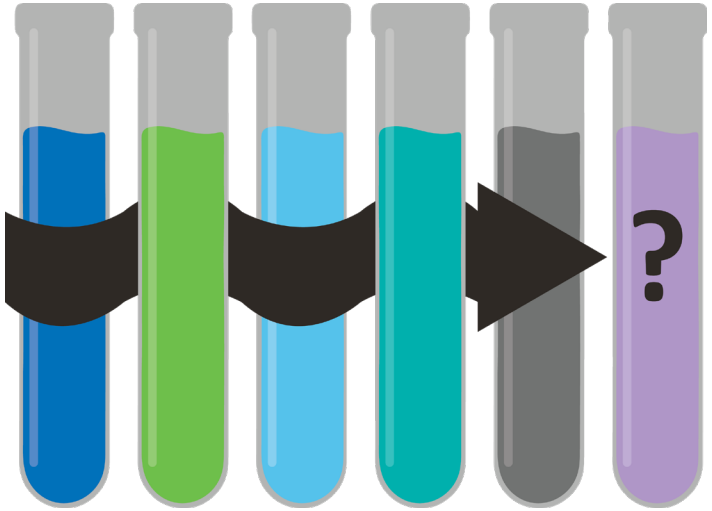
- Hazard assessment should be sufficiently detailed to support a hazard conclusion, but will need to balance available resources
- ALL hazard summaries should have a clear weight-of-evidence statement
- To improve consistency among complex evaluations and among staff, it is useful to develop a classification criteria protocol
- If chemical-specific data are not available, an attempt should be made to identify an appropriate chemical surrogate (*i.e.*,"read-across")
- Document references
- Understand confidence in conclusions
- Schedule updates
- Database preferable over spreadsheet

# Approach for Data-Rich Chemicals

- Data-rich chemicals have often been reviewed by authoritative agencies
  - Summarize conclusions
  - EFSA, SCCS, TSCA HPVs, IARC, NTC, OECD, *etc.*
    - Pay attention to date of publication
- For chemicals with data but no authoritative evaluation:
  - Present summary of study data and draw weight-of-evidence conclusions
    - REACH dossiers
    - Peer-reviewed literature???
    - OECD summaries

# Approach for Data Poor Chemicals

- Toxicity of a known (data-rich) chemical, called a "surrogate" or "analogue," is "read across" to a new (data-poor) chemical
  - Share key structural features
  - Common metabolite
- Guidance documents, tools
- If data based on a similar substance, can be noted on SDS



# Case Study: Read-Across

## Example 1: Use of Read-Across Assessment

**Issue:** Limited CAS-specific data

**Chemical of Interest:** Benzyl hexadecyl dimethyl ammonium chloride

| | Chemical of Interest | Chemical of Interest + Read-Across* |
|---|---|---|
| Hazard Conclusion | Acute Toxicity 4 Oral (H302); Skin Irritant 2 (H315) | Aquatic Acute 1 (H400); Aquatic Chronic 1 (H410); Acute Toxicity 4 Oral (H302); Acute Toxicity 3 Dermal (H311); Acute Toxicity 2 Inhalation (H330); Skin Irritant 1B (H314); Eye Irritant 1 (H318); STOT SE 3 (H335) |
| Rationale | No CAS-specific test data; Limited descriptions of toxicity | Test data in humans and animals; regulatory classifications (NZ) |
| Reference(s) | RTECS, TSCATS | REACH Dossier; LOLI Database; US EPA HPV; peer-reviewed literature |

**Benzyl C12-C16-alkyl dimethyl ammonium chlorides*

**Take Home:** If chemical-specific data are limited, use similar substances to inform the toxicity of the chemical of interest.

# Approach for Medium Data Chemicals: Animal Data Summary

- Summary by endpoint:
  - Study design, note if guideline study
  - Species tested
  - Study duration
  - All doses and exposure routes
  - No observable adverse effect level (NOAEL) and lowest observable adverse effect level (LOAEL)
  - References
    - If a website undergoes updates, save PDF at time of assessment

# Anatomy of a "Gold Standard" Weight-of-Evidence Statement

## Weight-of-Evidence Statements:

- If only one or several studies were used
- If the data are based on the compound of interest (COI) or a surrogate (and name of surrogate[s] if applicable)
- If the studies were conducted according to established guidelines
- Specific justification why a conclusion was reached if data are inconsistent
- Conclusions reached by other authoritative agencies

**"Weight of evidence" (WoE)** is the process of assembling, evaluating, and integrating all available scientific information to make a robust conclusion about a chemical hazard or risk

# Example Hazard Assessment

## Reproductive Toxicity (Including Developmental Toxicity

*Weight of Evidence: Based on the results of a reproductive/developmental screening study and of developmental toxicity studi Chemical X is considered to pose a clear developmental hazard in rats. Post-implantation loss was the critical adverse effect. In the guideline study the fetal LOAEL was 10 mg/kg-day, and no NOAEL was identified*

In a reproductive/developmental toxicity study (OECD 421), Wistar rats (n = 10/sex/dose) were administered 10, 50, and 200 mg/kg-day of the Chemical X (CAS No. XXX-X) *via* oral gavage for up to 53 days in dams. Clinical signs were observed in dams at 200 mg/kg-day. Body weight gain was less for both males and females at 200 mg/kg-day. At 200 mg/kg-day, post-implantation loss was 100%. At 50 mg/kg-day, there was an increase in the number of stillborn births. There was also elevated abnormalities in pups at 10 and 50 mg/kg-day. Since effects on the pups occurred at doses lower than where maternal toxicity occurred, these effects were considered adverse (ECHA, 2025). The parental LOAELs and NOAELs were 200 and 50 mg/kg-day, respectively; the fetal LOAEL was 10 mg/kg-day. No NOAEL was identified.

In a non-guideline study, female Sprague-Dawley rats were exposed to Chemical X *via* oral gavage at concentrations of 0, 20, 40 or 80 mg/kg-day during gestation days 6-19. The mean maternal adjusted body weight of the high-dose group was reduced in comparison to controls. There was a marked increase in the number of early resporptions and a corresponding increase in the number of post-implantation losses in the high-dose group. An increase in the number of fetuses and litters with unossified sternebrae was noted in the mid- and high-dose group compared to controls. Based on these findings, a developmental NOAEL of 20 mg/kg-day and LOAEL of 40 mg/kg-day was identified based on unossified sternebrae in the absence of maternal toxicity (US EPA, 2007).

The classification is further supported by GHS classifications as a Category 1 Reproductive Toxicant in Australia, EU, Japan, New Zealand, and Taiwan.

References:

European Chemicals Agency (ECHA). 2025. "REACH dossier for Chemical X (CAS XXX-X)." Accessed on April 06, 2025, at https://echa.europa.eu/cs/registration-dossier/-/registered-dossier/X.

United States Environmental Protection Agency, 2007. "Screening Level Evaluation of High Production Volume Chemicals: Chemica

# Example Weight of Evidence

| Reproductive Toxicity (Including Developmental Toxicity) |
| --- |
| **Weight of Evidence:** Based on the results of a reproductive/developmental screening study and of developmental toxicity studies in rats, chemical X is considered to pose a developmental hazard. Post-implantation loss was the critical adverse effect. In the key guideline study, the fetal LOAEL was 10 mg/kg-day, and no NOAEL was identified. |

# Example Detailed Support

## Reproductive Toxicity (Including Developmental Toxicity)

In a reproductive/developmental toxicity study (OECD 421), Wistar rats (n = 10/sex/dose) were administered 10, 50, and 200 mg/kg-day of the chemical X (CAS No. XXX-X) *via* oral gavage for up to 53 days in dams. Clinical signs were observed in dams at 200 mg/kg-day. Body weight gain was less for both males and females at 200 mg/kg-day. At 200 mg/kg-day, post-implantation loss was 100%. At 50 mg/kg-day, there was an increase in the number of stillborn births. There was also elevated abnormalities in pups at 10 mg/kg-day. Since effects on the pups occurred at doses lower than where maternal toxicity occurred, these effects were considered adverse (US EPA, 2016). The parental LOAELs and NOAELs were 200 mg/kg-day and 50 mg/kg-day, respectively; the fetal LOAEL was 10 mg/kg-day. No NOAEL was identified.

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The classification is further supported by GHS classifications as a Category 1 Reproductive Toxicant in Australia, EU, Japan, New Zealand, and Taiwan.

# Example References

## Reproductive Toxicity (Including Developmental Toxicity)

**References:**

European Chemicals Agency (ECHA). 2025. "REACH dossier for Chemical X (CAS-XXX-X)." Accessed on April 06, 202 at https://echa.europa.eu/cs/registration-dossier/-/registered-dossier/X.

United States Environmental Protection Agency (US EPA). 2007. "Screening Level Evaluation of High Production V Chemicals: Chemical X."

# Keeping Up with Emerging Toxicity Information

- Many programs available for keeping up with regulations
- New authoritative assessments
  - EFSA, SCCS, TSCA priority assessments
- Peer-reviewed literature
- Dossiers and Public Activities Coordination Tool (PACT)

# Emerging Toxicity Information

## PACT - Public Activities Coordination Tool

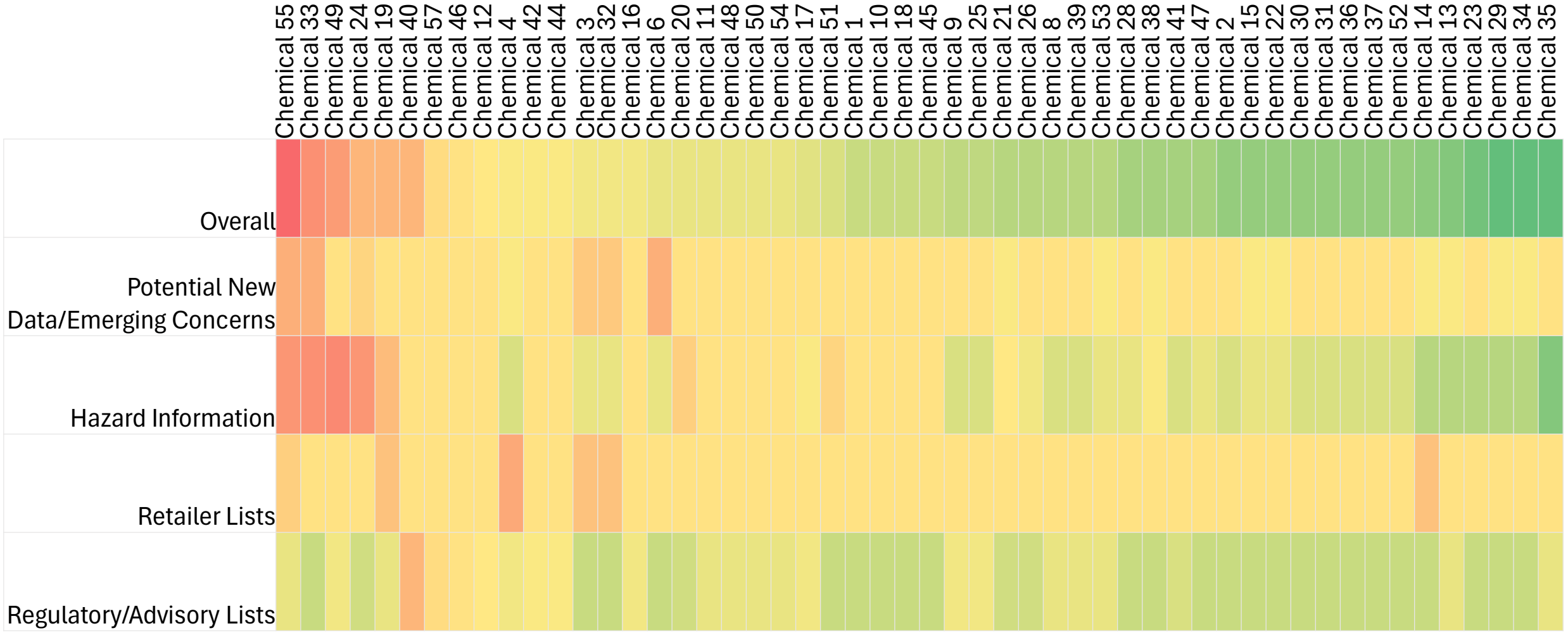
The public activities coordination tool (PACT) provides an overview of the substance-specific activities that authorities are working on under REACH and the CLP Regulation. These activities are being carried out in line with ECHA's Integrated Regulatory Strategy.

PACT provides up-to-date information on the activities planned, ongoing or completed by ECHA and/or MSCAs for a given substance in the following areas:

- Data generation and assessment – dossier evaluation, substance evaluation, informal hazard assessment (PBT/vPvB/ED).
- Assessment of regulatory needs (ARN).
- Regulatory risk management – harmonised classification and labelling (CLH) , SVHC identification, recommendations for inclusion in the Authorisation List, restriction.

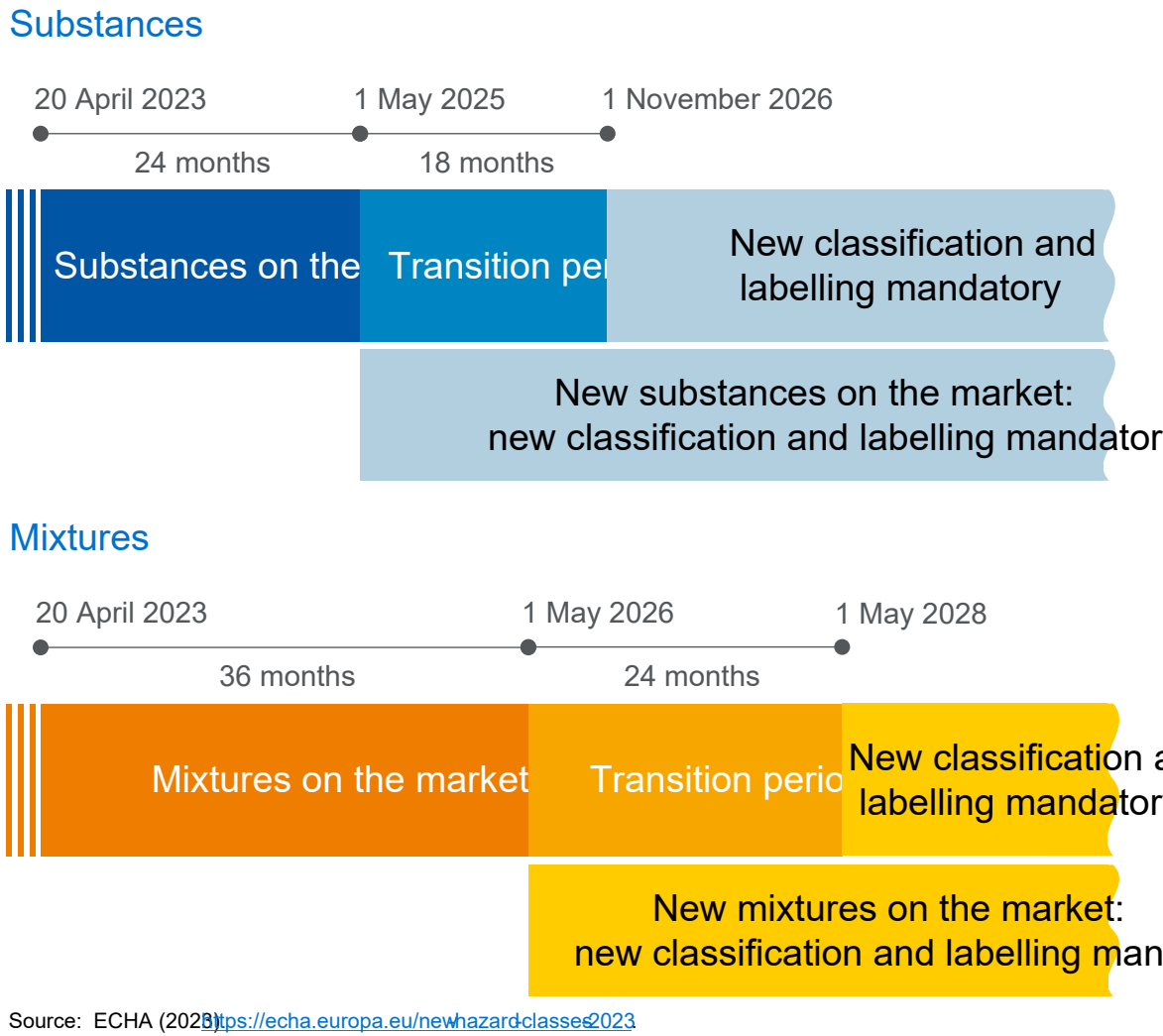
A summary of all the substance-specific activities can be found under 'Details' for each entry.

# Conduct Vulnerability Assessment



# Recent Regulatory Developments in the EU: New CLP Hazard Classes

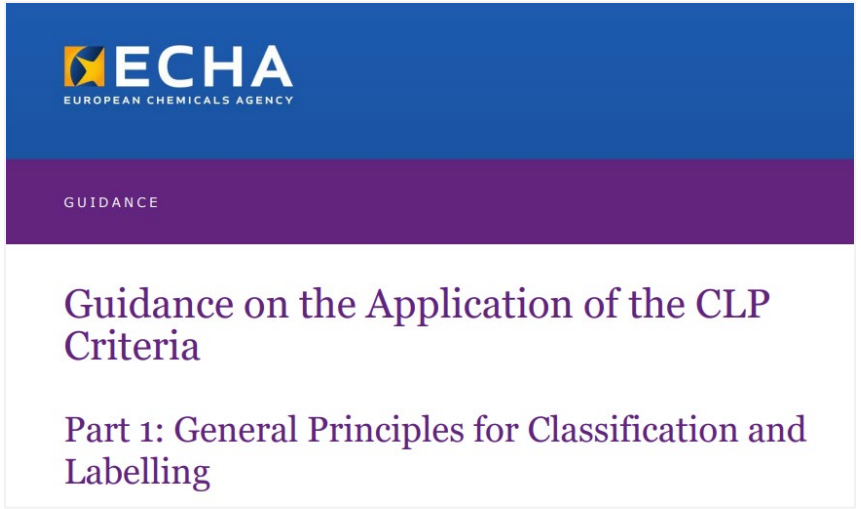
- Regulation (EC) No 1272/2008 on CLP of substances and mixtures
- New hazard classes proposed in 2022
  - Endocrine-Human Health & Environment
  - PBT/vPvB and PMT/vPvM
- Final guidance November 2024
- Transition period for reclassification and labelling of substances and mixtures
- **CLP anticipated to become a key regulatory driver for evaluating endocrine disruption (ED) in the coming years**

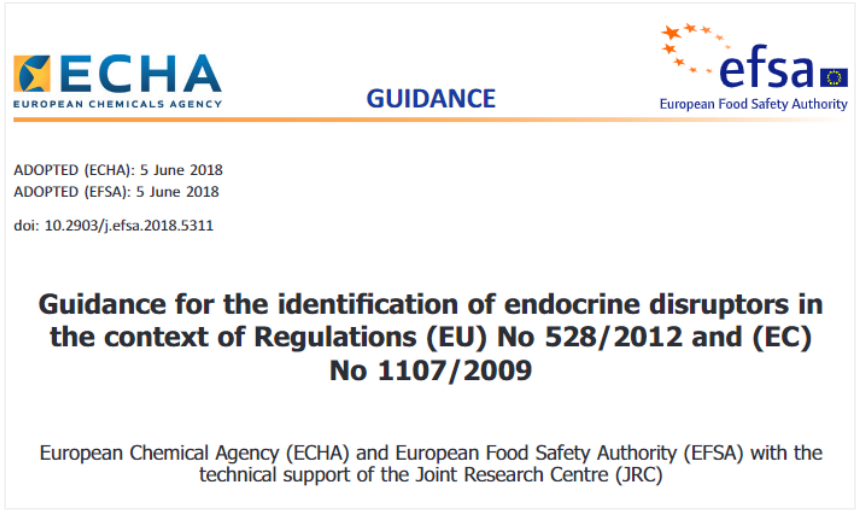



Source: ECHA (2023) https://echa.europa.eu/new-hazard-classes-2023

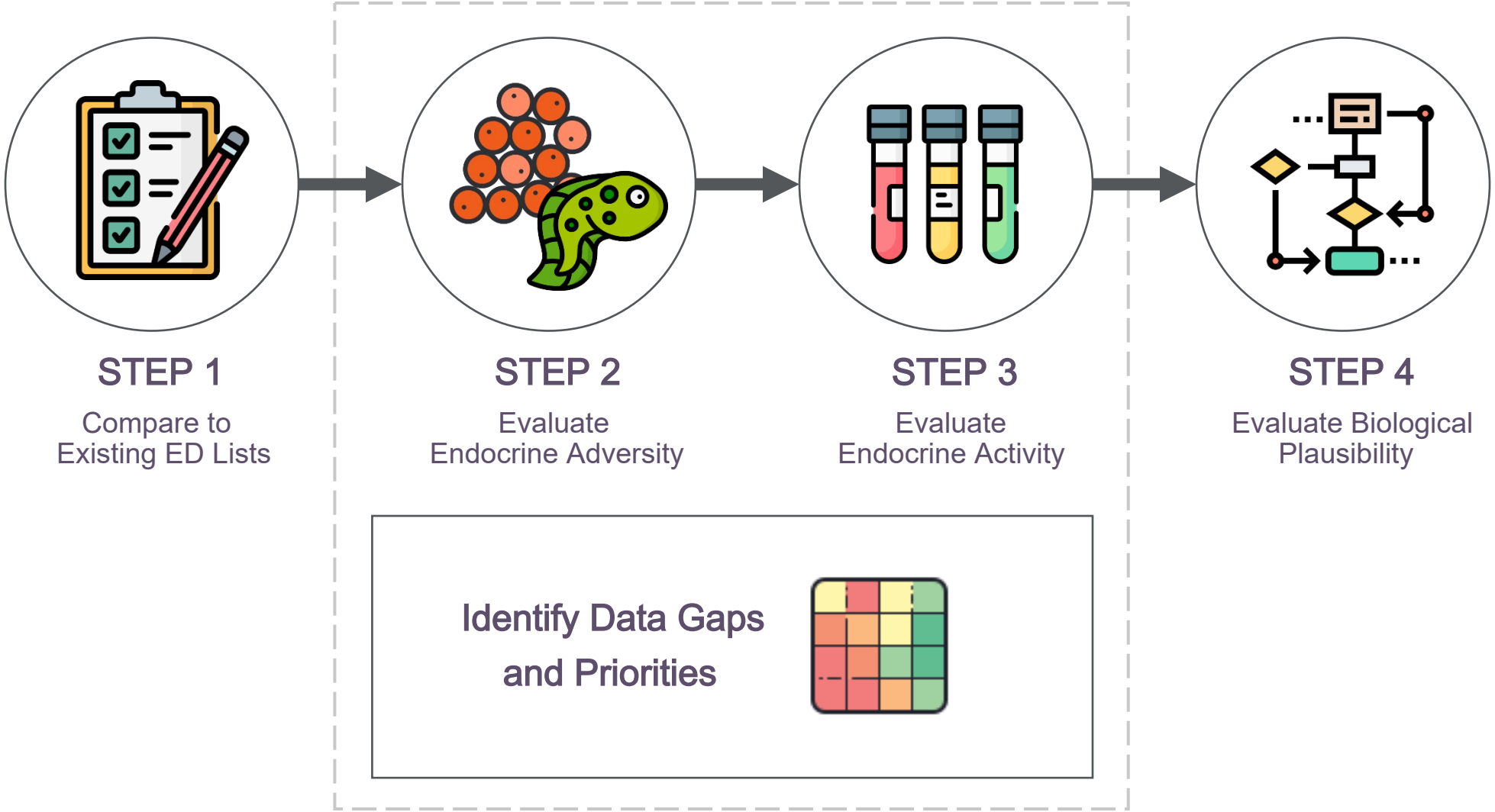
# Evaluating Your Ingredient Portfolio

- Impact to regulated community could be substantial
- Evaluate portfolio by relying on:
  - Draft CLP guidance
  - EFSA/ECHA guidance for BP and PPP
  - OECD Conceptual Framework for EDs
- REACH testing requirements not promulgated yet
  - But there is a self classification template in IUCLID

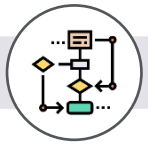


# Evaluating Your Ingredient Portfolio for ED



# Compare to Existing ED Lists

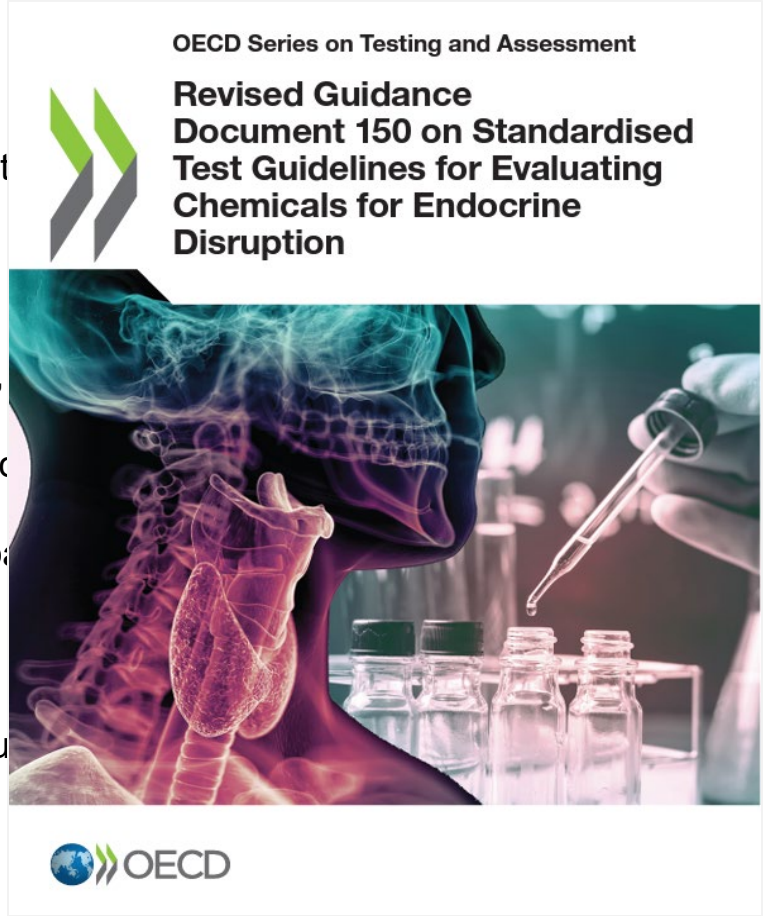
STEP 1  STEP 2  STEP 3  STEP 4 

- Certain EU ED assessments are adequate to classify under CLP
  - ED under BP/PPP procedures → Assigned ED HH 1 and ED ENV 1 in CLP
  - SVHC for ED under REACH → Assigned ED HH 1 and ED ENV 1 in CLP
- Other screening lists
  - ECHA's ED Assessment list (https://echa.europa.eu/ed-assessment)
  - Candidate list of SVHC for ED under REACH (https://www.echa.europa.eu/candidate-list-table)
  - ED lists (https://edlists.org/the-ed-lists)
  - UNEP lists (https://wedocs.unep.org/bitstream/handle/20.500.11822/25633/EDC_report1.pdf?sequence=1&isAllowed=y)
  - ChemSec SIN list (https://sinlist.chemsec.org/endocrine-disruptors/)
  - Japan SPEED '98 list (https://www.env.go.jp/en/chemi/ed/speed98/sp98t3.html)
  - TEDX list (https://endocrinedisruption.org/interactive-tools/tedx-list-of-potential-endocrine-disruptors/search-the-tedx-list)

# Evaluate Existing Endocrine **Adversity** Data (Human Health)

STEP 1 | STEP 2 | STEP 3 | STEP 4

| OECD Level | Test/Data Type | Example Endpoints |
|---|---|---|
| **Level 3** | • Uterotrophic bioassay in rodents<br>• Hershberger bioassay (H assay) | • Possible liver weight increase (in combination wit thyroid-related endpoints)<br>• Changes in serum T4 and T3 |
| **Level 4** | • 28/90-day repeated dose study<br>• Reproduction/developmental toxicity screening test<br>• Combined chronic toxicity and carcinogenicity studies | • Changes in sperm parameters: sperm numbers, sperm morphology<br>• Histopathologic changes in the above organs and glands<br>• Serum T4, T3 decreased, TSH increased; histopa in thyroid gland |
| **Level 5** | • Extended-generation reproductive toxicity study<br>• Two-generation reproduction toxicity study | • Litter size, sex ratio (F1, F2), litter/pup weight, pu index, abnormalities in pup development<br>• Anogenital distance |



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# Evaluate Endocrine **Activity** (Human Health and Environment)

STEP 1 | STEP 2 | **STEP 3** | STEP 4

## Activity Assessment

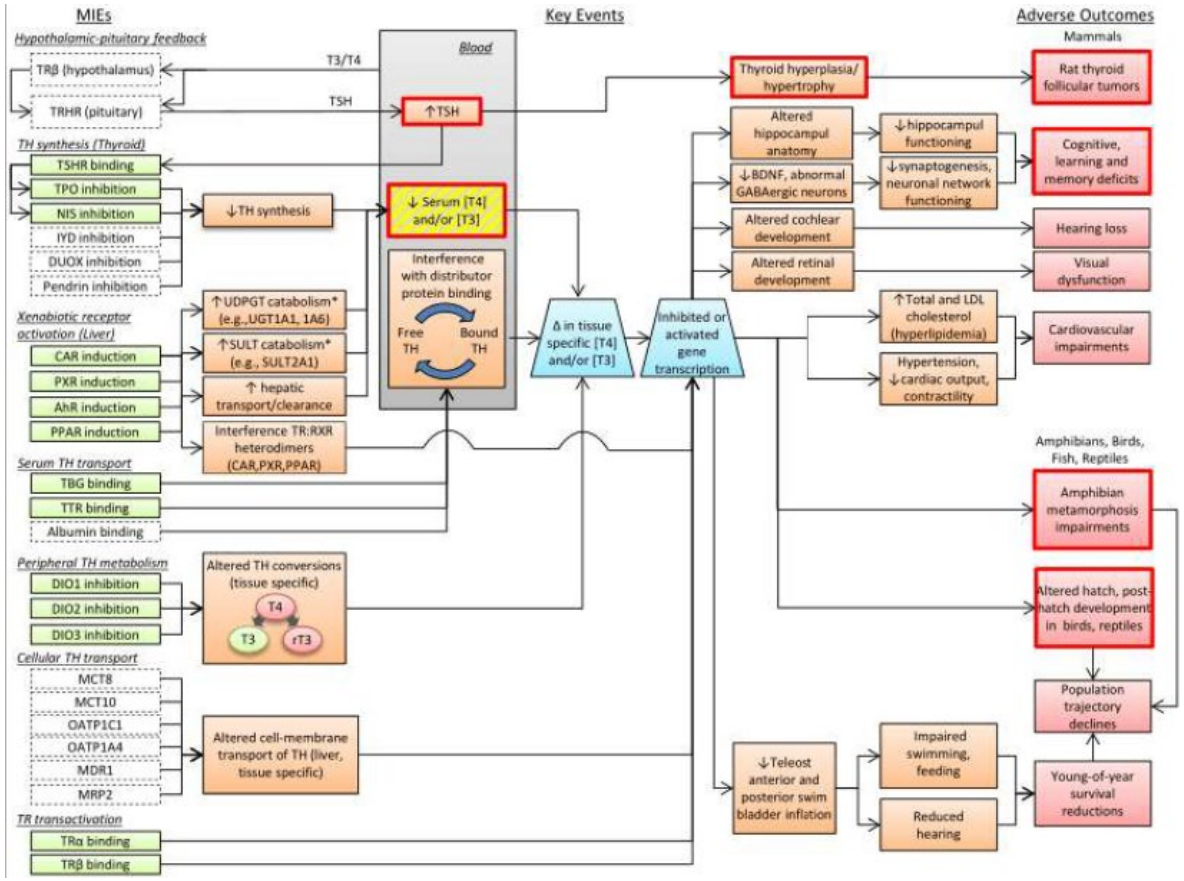
| OECD Level | Test/ Data Type | Example Information |
|---|---|---|
| **Level 1** | Existing data and non-test information | • Physical and chemical properties<br>• All available (eco)toxicological data from (non-) standardized tests<br>• Read-across, chemical categories, QSARs, *in silico* prediction<br>• Scientific literature |
| **Level 2** | *In vitro* mechanistic assays (mammalian and non-mammalian methods) | • ER/AR binding and transactivation assay<br>• Steroidogenesis *in vitro*<br>• Aromatase assay<br>• Thyroid disruption assays<br>• High-throughput screens |

## Primary Data Sources

- US EPA's ToxCast™
- US EPA's Collaborative Estrogen Receptor Activity Prediction Project (CERAPP)
- US EPA's Collaborative Modeling Project for Androgen Receptor Activity (CoMPARA)
- QSAR DataBank (QsarDB)
- Danish (Quantitative) Structure-Activity Relationship [(Q)SAR] Database

# Evaluate Biological Plausibility

STEP 1 | STEP 2 | STEP 3 | STEP 4




Source: ECHA (2017) Microsoft Word - CLP_Guidance_ED_revised_with_headings.docx (europa.eu)

- Evaluate **biological plausibility** only for key ingredients
  - Can be a significant effort
  - Requires expert judgment
  - Relies on mode of-action and weight-of-evidence approach
  - Analogy, essentiality, consistency, specificity, temporal concordance

# Take Homes

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- A hazard assessment you can stand by can be difficult and resource intensive
- Many resources out there for getting toxicity information to inform assessment
- Proper documentation is key
- Toxicity information is evolving, and periodic updates are important
- New CLP hazard classes may pose unique challenges

# Thank You!


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