Development of Acute to Chronic Ratios (ACRs) Applicable to Surfactant Ecotoxicity

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Introduction and aims

Surfactants find extensive use within a variety of settings, both domestic and industrial

- The presence of gaps within historical ecotoxicological data for some surfactants hinders the regulatory evaluation of their associated environmental risk
- Across all trophic levels, coverage with respect to chronic endpoints can be lacking

Acute-chronic ratios (ACR) assist in understanding chronic toxicity without the need for animal use, and thus accord with 3R principles for uptake of new approach methodologies (NAM) within risk assessment

- Derived from existing pool of corresponding experimental short- and long-term adverse outcome data
- Applied for purposes of extrapolating known toxic potencies (i.e., acute) to unknown (chronic)

Derivation

$$ACR = \frac{\text{Acute tox.}(\text{measured})}{\text{Chronic tox.}(\text{measured})}$$

Training dataset

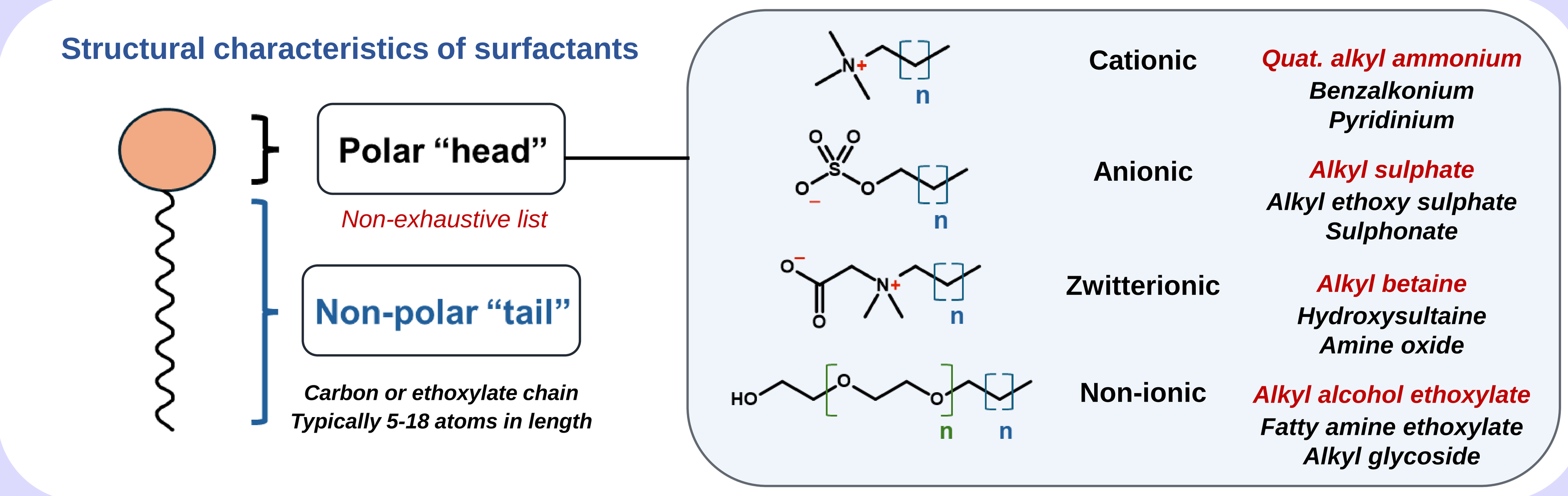
Application

$$\text{Chronic tox.}(\text{estimated}) = \frac{\text{Acute tox.}(\text{measured})}{ACR}$$

Where only acute toxicity is established

The feasibility of adopting ACR methodology within such substances remains unestablished

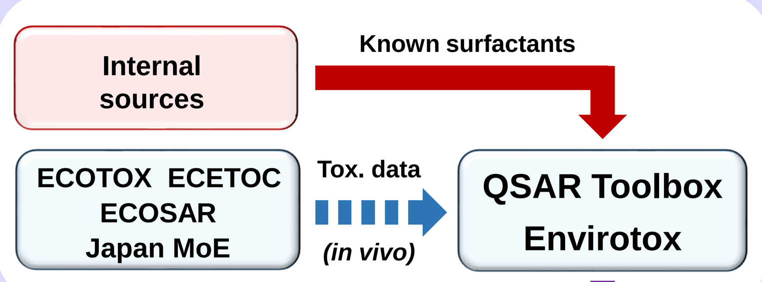
- Previously-reported surfactant ACR do not account for all classes
- Supporting data used in their derivation are not available so cannot be replicated or evaluated



Sourcing existing ecotoxicological data, we sought to develop robust, transparent surfactant-exclusive ACRs

- The suitability and consistency of the approach is examined within fish, daphnid and algal species
- Acquired ratios are employed for purposes of estimating chronic toxicity within a validation set

Materials and methods



Inventory of >1500 acknowledged surfactants (alongside CAS and structural ID), representing all major classes

Associated aquatic toxicity data *(in vivo)* acquired from OECD QSAR Toolbox and Envirotox resources

Preliminary dataset curated and filtered, such that only high quality outcomes described beneath were retained

Preliminary dataset

Fish

All teleost species

Acute

Duration: 96 hour (exclusively)
Endpoint: EC50, LC50
Effect: Lethality

Chronic

Duration: ≥ 21 days
Endpoint: EC10 > EC20 > NOEC
Effect: Reproduction (preferred)

Daphnid

D. magna, C. dubia

Acute

Duration: 48 hour (exclusively)
Endpoint: EC50, LC50
Effect: Immobilisation, lethality

Chronic

Duration: ≥ 21 days (*D. magna*)
7 days (*C. dubia*)
Endpoint: EC10 > EC20 > NOEC
Effect: Reproduction (preferred)

Algae

Common test species

Acute

Duration: 72 or 96 hour
Endpoint: EC50
Effect: Growth rate (preferred)

Chronic

Duration: 72 or 96 hour
Endpoint: EC10 > EC20 > NOEC
Effect: Growth rate (preferred)

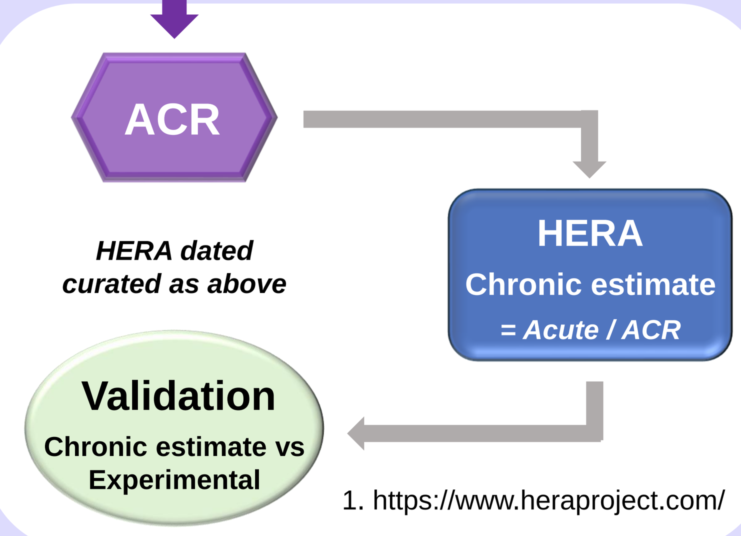
Curated dataset

Acute and chronic data, post-curation, was matched in accordance with substance CAS ID and test species

Where multiple outcomes described a single CAS and species combination, geometric mean acute or chronic values were taken prior to ACR calculation

Validation was performed against a test set, consisting of surfactant data sourced through efforts of the Human and Environmental Risk Assessment (HERA) initiative [1]

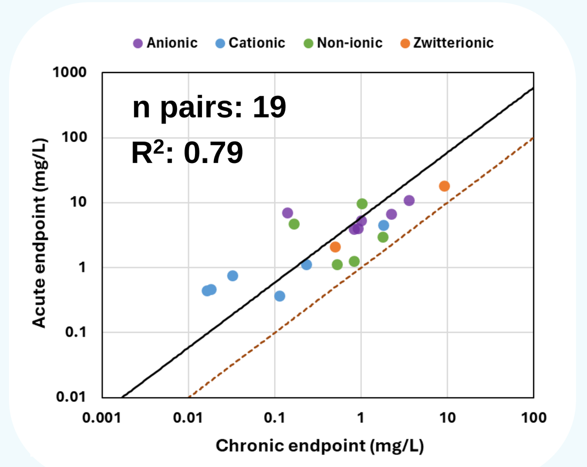
Chronic toxicity estimates, acquired through ACR extrapolation of acute output, were compared relative to their recorded experimental counterparts



1. https://www.heraproject.com/

Surfactant acute-chronic toxicity relationships

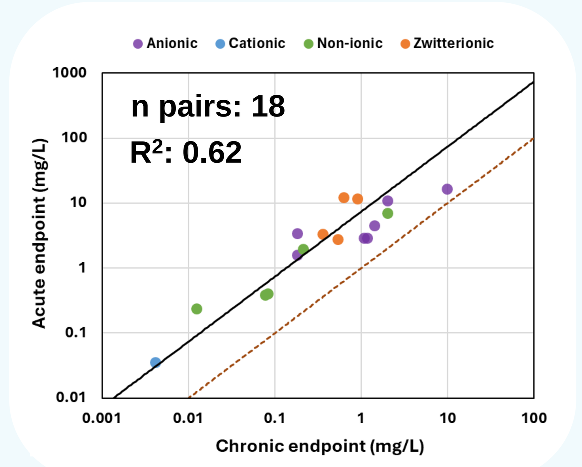
Fish



ACR

Median: 4.45 90%: 27.4
Minimum: 1.55 Maximum: 50.7

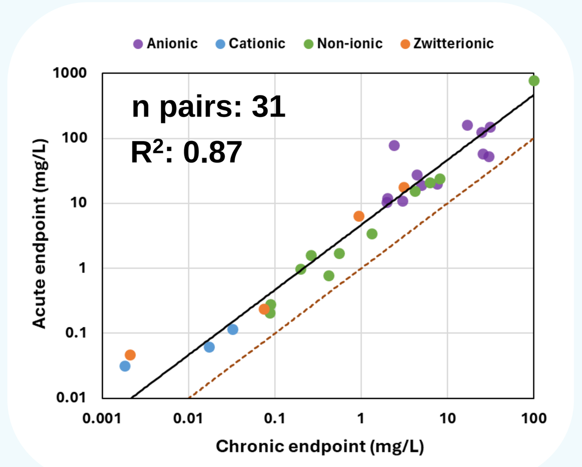
Daphnid



ACR

Median: 7.09 90%: 19.4
Minimum: 1.69 Maximum: 78.7

Algae



ACR

Median: 3.80 90%: 9.40
Minimum: 1.77 Maximum: 32.4

Plotted points represent eligible acute-chronic pairings (shared CAS identifier). Line (solid): Regression trend. Line (dotted): ACR = 1

At each trophic level, key outcomes with respect to relationship between acute-chronic toxicity are presented

- Ranging from 3.80 to 7.10, median ACR was broadly comparable within fish, daphnids and algae
- A higher figure, 16.0, was associated with cationic surfactants (albeit with smaller sample size, n = 7)
- General variability in terms of acute-chronic correlation appeared at its lowest within algae (R^2 = 0.87)
- Isolated outliers were nevertheless present at all levels (e.g., with maximal daphnid ACR reaching 78.7)

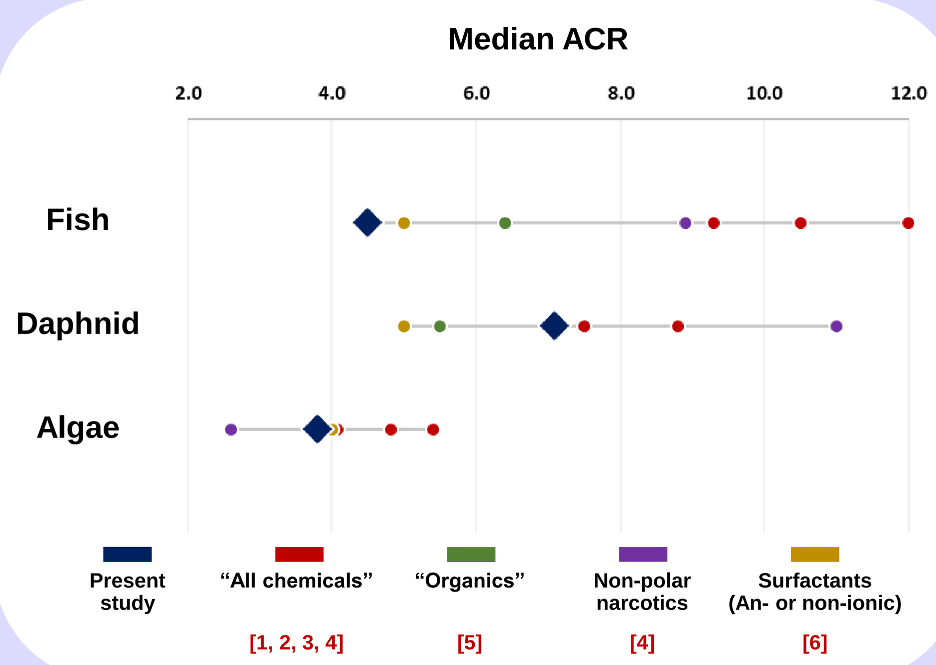
Placement relative to historical studies

So that these outputs might be viewed within broader context, ACRs relating to alternative substance classes were sourced from literature

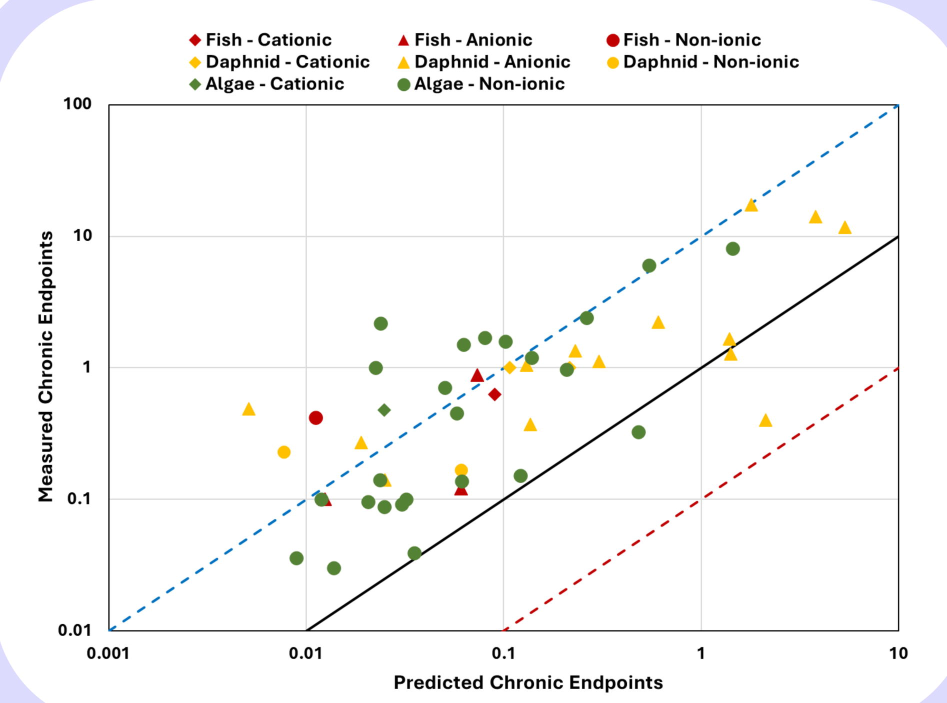
- Both daphnid and algal median ACRs lay central within the ranges of those associated with other chemical forms
- Derived fish ACR sits at the lower end of the range but aligns well with previously reported nonionic anionic surfactant ratios

Study origins:

1. Raimondo et al., 2007
2. May et al., 2016
3. Brill et al., 2021
4. Alher et al., 2006
5. ECETOC, 2003
6. US EPA, 2012



Validation of ACR as chronic toxicity estimation tool



The accompanying plot illustrates alignment between measured and ACR-estimated chronic values (95th percentile, HERA test set)

- Of 48 predictions, 45 were shown to exhibit conservativeness relative to experimental (i.e., appeared leftwards of solid line)
- From this 45, a total of 32 were over-predictive within the range of a single order of magnitude (i.e., within blue dotted line)
- Algal outcomes accounted for 25/48 data points, daphnid for 18/48 and fish (lacking in chronic entries) for 5/48
- Sample size relating to all but algae (non-ionic) and to daphnid (anionic) was insufficient for enabling deeper analysis

Discussion and conclusions

Adopting historical data drawn from test species representative of three ecologically-relevant trophic levels, the applicability of the ACR principle towards common surfactant classes was demonstrated

- Median ACRs align with those sourced from literature in relation to alternative chemical classes
- Evaluation of a surfactant test set indicated these ratios to produce, in the great majority of instances, protective estimates of chronic toxicity
- Extent of curation yields datasets which are selective in scope, consisting of smaller (albeit sufficient for statistical robustness) quantities of high-quality data
- Presence of outliers is likely indicative of challenges associated with the necessary comparison of acute and chronic outcomes derived from studies conducted according to differing test protocols
- On occasion, relevant details may remain unreported or else otherwise inaccessible
- Elevated ACRs observed within cationic surfactants may well arise as a consequence of the above
- Such issues were not prominent when considering algal data, owing to the tendency for both short- and long-term toxicity endpoints to be examined and reported in parallel

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