Simple Assessment-Factor Based PNEC Estimation: Using Order Statistics

Graeme Hickey[1*], Peter Craig[1] & Andy Hart[2]
[1]Durham University, Dept. of Mathematical Sciences, Durham, UK
[2]The Food and Environment Research Agency, York, UK
*Email: g.l.hickey@durham.ac.uk

Available data	Assessment factor
At least one short-term L(E)C50 from each of three trophic levels of the base set (fish, *Daphnia*, algae)	1000
One long-term NOEC (either fish or *Daphnia*)	100
Two long-term NOECs from species representing two trophic levels of the base set (fish and/or *Daphnia* and/or algae)	50
Long-term NOECs from at least three species (normally fish, *Daphnia*, algae) representing three trophic levels	10
Species sensitivity distribution (SSD) method	5-1
Field data or model ecosystems	Reviewed on a case by case basis

Table 1 (above). Assessment factors for deriving a PNEC for aquatic compartments exposed to industrial substances (REACH TGD, p. 19, Table R.10-4). The latest guidance provides clarification on the sources of uncertainty assessment factors are intended to account for, namely:
- intra- and inter-laboratory variation of toxicity data;
- intra- and inter-species variation (biological variance);
- short-term to long-term toxicity extrapolation;
- laboratory data to field impact extrapolation.

Fields shaded indicate different (non-order statistic) PNEC derivation tools.

- The standard risk assessment approach for exposure of aquatic ecosystems to plant protection products (PPPs) is based on (using standard REACH notation in the interest of generality) the Risk Characterisation Ratio (RCR):

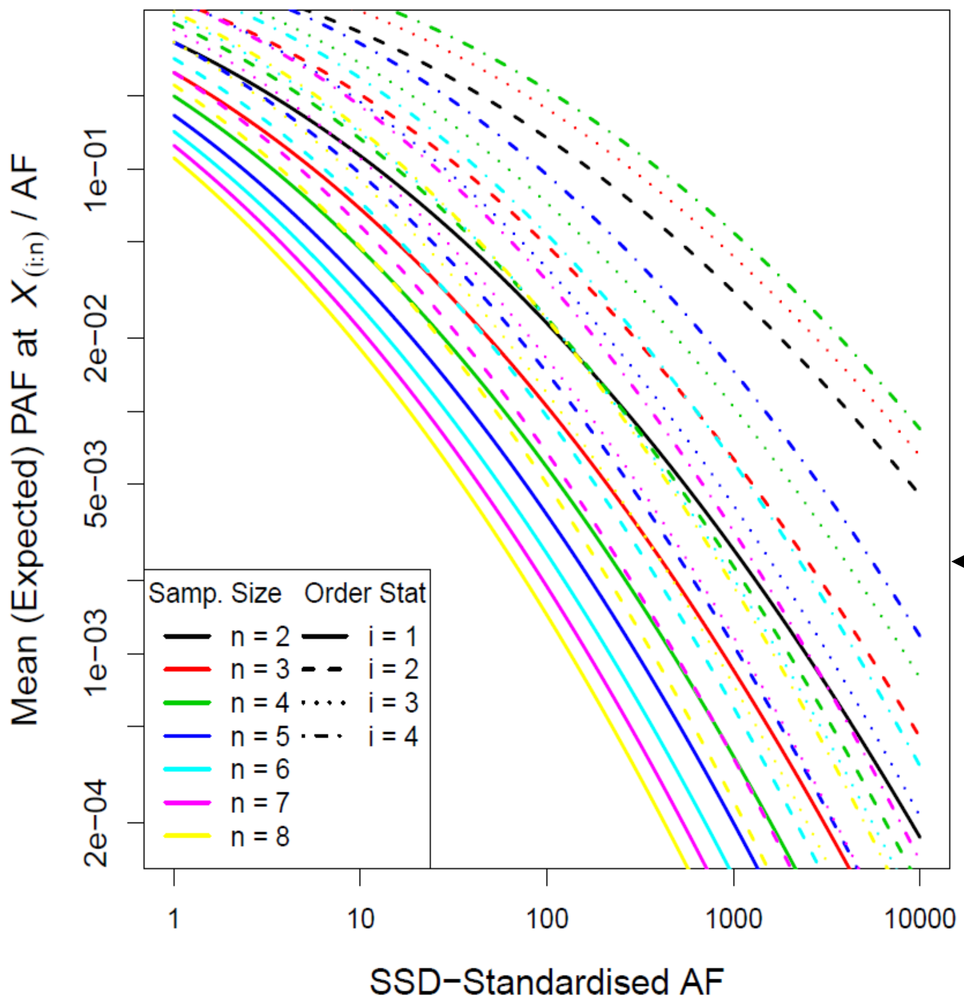
$$\text{RCR} = \frac{\text{PEC}}{\text{PNEC}}$$

NB. PPP technical guidance actually uses the term 'Toxicity Exposure Ratio' (TER), such that: TER = AF / RCR.

- PNEC = Predicted No Effect Concentration and PEC = Predicted Exposure Concentration.
- **Notation:** $X_1, \ldots, X_n$ are a collection of n toxicity test results (acute EC_{50} or long-term NOEC) for a pesticide. Let $X_{(i:n)} = i$-th numerically ranked value.

If $X_{\text{Rainbow trout}} = 1.2$ mg/L, $X_{\text{Atlantic salmon}} = 12.5$ mg/L, $X_{\text{Shortnose sturgeon}} = 5.9$ mg/L and $X_{\text{Threespine stickleback}} = 8.4$ mg/L are $n = 4$ observed LC_{50} values for a hypothetical pesticide, then $n = 4$, $X_{(1:4)} = 1.2$, $X_{(2:4)} = 5.9$, $X_{(3:4)} = 8.4$ and $X_{(4:4)} = 12.5$.

- Current practice defines PNEC = $X_{(1:n)}$ / AF — the minimum result from a sample of n (with n usually 1 or 2) divided by an assessment factor (AF) provided in Directive 91/414/EEC, Annex VI.
- **Decision Making Criterion:** If the RCR is greater than one, then authorisation may not be granted unless an appropriate (higher tier) risk assessment demonstrates that the risk is acceptable.
- Current level of protection implied by the RCR is undefined.
- Testing more species leads to an increasingly more conservative risk assessment if the assessment factor remains fixed.



- Part of the fixed assessment factor is intended to account for interspecies variation.
- The Species Sensitivity Distribution (SSD) probabilistically models interspecies variation. For a defined assemblage of biological species, the SSD predicts the potentially affected fraction (PAF) of species for any given environmental concentration.
- The SSD is generally accepted for regulatory application when $n \geq 8$-10 (REACH TGD, HARAP).
- Define the Generalised PNEC = $X_{(i:n)}$ / AF for $n \geq 2$, i.e. the i-th numerically ranked toxicity test result for a sample of 3 or more.
- The statistically expected [mean] PAF for any Generalised PNEC can be determined with respect to a theoretical SSD shape, e.g. log-normal (cf. EFSA, 2005) or log-logistic.
- **Figure 1 (left):** Interpolated plot of mean PAF when PNEC = $X_{(i:n)}$ / AF for various choices of i and n, against 'SSD-standardised' assessment factors for a theoretical log-normal SSD.
- For fish, standard practice is to set PNEC = $X_{(1:2)}$ / AF. Figure 1 implies setting PNEC as $X_{(2:5)}$ / AF [blue-dashed curve] or $X_{(3:8)}$ / AF [yellow-dotted curve] yields a mean PAF uniformly bounded by the current level of protection [black-solid curve].

Key Developments of EFSA (2005)

- The revised PNEC estimates are shown to be robust for many "near normal" log-SSDs, e.g. logistic, skew-normal, exponential power and positive skewed bimodal distributions (Hickey, 2010).
- Conclusions are strengthened by stronger analytical evidence based on theory of (Second Order) Stochastic Dominance (Hickey, 2010).
- Demonstrates mutual benefit between regulators and industry if more data is available for risk assessment.

Conclusion

If it is reasonable to assume a collection of n distinct species toxicity values are a random sample from an (unknown) 'near-normal' log-SSD, then the RCR decision criterion is statistically expected to provide *at least* the current (undefined) level of protection implied when based on the Generalised PNEC given by:

$$\text{PNEC} = \begin{cases} X_{(1:n)} / \text{AF} & \text{for } 2 \leq n \leq 4; \\ X_{(2:n)} / \text{AF} & \text{for } 5 \leq n \leq 7; \\ X_{(3:n)} / \text{AF} & \text{for } 8 \leq n \leq 10; \\ \text{HC}_5 / \text{AF}_{\text{SSD}} & \text{with appropriate AF}_{\text{SSD}} \text{ for sufficiently large } n. \end{cases}$$

References

EFSA (European Food Safety Authority) 2005. Assessment of the Acute and Chronic Risk to Aquatic Organisms with Regard to the Possibility of Lowering the Uncertainty Factor if Additional Species were Tested, The EFSA Journal, 301: 1-45.

HARAP (Guidance Document on Higher Tier Aquatic Risk Assessment for Pesticides) 1999. Campbell, PJ, Arnold, DJS, Brock, TCM, Grandy, NJ, Heger, W, Heimbach, F, Maund, SJ and Streloke, M Eds. Brussels: SETAC.

Hickey, GL. 2010. Ecotoxicological Risk Assessment: Developments in PNEC Estimation. Ph.D. Thesis. Durham University, UK.

REACH TGD (European Chemicals Agency) 2008. Guidance on Information Requirements and Chemical Safety Assessment Chapter R.10: Characterisation of Dose-Response for Environment. July 2008.