Assessing the Value of Including Sediments in OECD 106 Studies for Pharmaceutical Environmental Risk Assessments.

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Environmental risk assessment (ERA) of human medicines focuses on exposure pathways associated with 'down the drain' chemicals, i.e. those that enter wastewater treatment plants and subsequently surface waters, or the terrestrial environment via application of sewage sludge to land.

The target environmental compartment ultimately depends on the partitioning behaviour between aqueous and solid media, in wastewater treatment, then between surface water and sediment (aquatic compartment) and/or between soil and porewater (terrestrial compartment).

The new European Medicines Agency (EMA) ERA guideline requires an OECD 106 test for adsorption to sludge and soils.

The role of sediment testing is less clear, although in the previous (2006) EMA ERA Guideline, no preference was given to soils or sediment, thus many OECD 106 studies had included sediments, given that partitioning coefficients derived using sediments are arguably more relevant than those derived using soils, for calculating potential sediment exposure.

To explore the value or otherwise of including sediments, historical adsorption data on pharmaceuticals was reviewed for:

- The importance of organic carbon or other drivers of partitioning of pharmaceuticals and if, or when, corrections for organic carbon content are appropriate
- The utility of the Input Decision (I.D.) tool recommended for use in the EMA ERA Guideline
- Whether soil and sediment data can be 'pooled' for the purpose of calculating geometric means and implications for the sediment compartment risk assessment

24 active pharmaceutical ingredients (APIs) with OECD 106 data for different soils and/or sediments were analysed using the I.D. tool recommended by EMA (EMA, 2024)
- 4 APIs had soil adsorption data only (n=4 or 5)
- 20 APIs had adsorption data for 2 soils and 2 sediments (n=4)

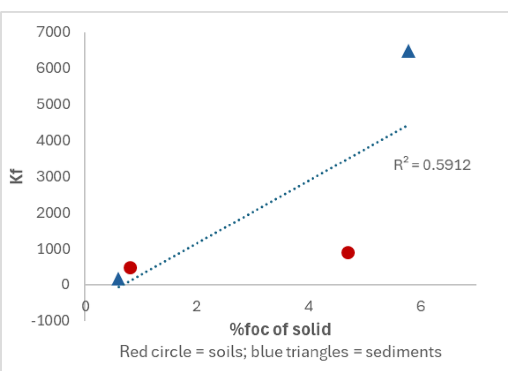
API No.	Dataset	Predominant Speciation (based on pKa values and ACD Labs- Percepta)	Excel R^2 Linear relationship with OC	Input Decision output: K_F correlation with OC	K_F correlation with CEC	K_F CV	$K_{F,OC}$ CV	Recommended parameter
1	2 soils, 2 seds	Neutral - HOM soil and seds Cation (+1) - LOM soil	Kd – 0.022 Kf – 0.003	N	N	84	144	Mean Kf
2	2 soils, 2 seds	Neutral	Kd – 0.094 Kf – 0.446	N	N	49	90	Mean Kf
3	2 soils, 2 seds	Cationic (+1) - HOM soil, seds (+2) - LOM soil	Kd – 0.303 Kf – 0.439	N	N	60 (Kd) 186 (Kf)	162 (Kd) 108 (Kf)	**(Mean Kd)*** Kf 90%-ile
4	2 soils, 2 seds	Neutral - HOM soil Cationic (+1) - LOM soil Cationic/neutral - seds	Kd – 0.008 Kf – 0.064	N	N	83	142	Mean Kf
5	2 soils, 2 seds	Cationic (+1)	Kd – 0.316 Kf – 0.039	N	N	93	146	Mean Kf
6	2 soils, 2 seds	Neutral	Kd – 0.637 Kf – 0.348	N	N	50	82	Mean Kf
7	2 soils, 2 seds	Neutral - HOM soil and seds Cationic (+1) - LOM soil	Kd – 0.185 Kf – 0.271	N	N	79	128	Mean Kf
8	2 soils, 2 seds	Cationic (+1) - HOM soil +2/+1 - LOM soil and seds	Kd – 0.497 **Kf – 0.938**	N	N	88	38	Mean Kf,oc
9	2 soils, 2 seds	Neutral	**Kd – 0.94** **Kf – 0.833**	**Y (Kd)** N (Kf)	N (Kd) Y (Kf)	105 (Kd) 103 (Kf)	50 (Kd) 59 (Kf)	(**Mean Koc**)* Mean Kf,oc
10	2 soils, 2 seds	Neutral	**Kd – 0.741** **Kf – 0.765**	N	N	97	35	Mean Kf,oc
11	2 soils, 2 seds	Neutral	**Kd – 0.766** **Kf – 0.9398**	N (Kd) **Y (Kf)**	N	107	34.8	Mean Kf,oc
12	2 soils, 2 seds	Neutral	Kd – 0.295 Kf – 0.426	N	N	100	67	Mean Kf
13	2 soils, 2 seds	Neutral	Kd – 0.658 **Kf – 0.8**	N	N	116 (Kd) 109 (Kf)	74 (Kd) 64 (Kf)	Kf 90%-ile
14	2 soils, 2 seds	Anionic (-1)	Kd – 0.603 Kf – 0.591	**Y (Kd)** **Y (Kf)**	N	154 (Kd) 150 (Kf)	89 (Kd) 80 (Kf)	Mean Kf,oc
15	2 soils, 2 seds	Neutral	Kd – 0.577 **Kf – 0.995**	N	N	105	36	Mean Kf,oc
16	3 soils, 2 seds	Cationic (+1)	Kd - 0.581 Kf – 0.373	**Y (Kd)** N (Kf)	N (Kd) Y (Kf)	114 (Kd) 79 (Kf)	72 (Kd) 89 (Kf)	(**Mean Koc**)* Mean Kf,oc
17	2 soils, 2 seds	All neutral	Kd – 0.481 Kf – 0.294	N	N	120 (Kd) 136 (Kf)	71 (Kd) 80 (Kf)	(**Kd 90%-ile**)* Kf 90%-ile
18	2 soils, 2 seds	All neutral	**Kd – 0.972** **Kf – 0.947**	**Y (Kd)** **Y (Kf)**	N	85 (Kd) 75 (Kf)	36 (Kd) 30 (Kf)	Mean Kf,oc
19	2 soils, 2 seds	Cationic (+1) +1/zwitterion - HOM soil	Kd – 0.179 No Kf	N	N	37	63	Mean Kd
20	2 soils, 2 seds	Cationic (+1)	Kd – 0.289 Kf – 0.692	N	Y	69	98	Mean Kf
21	5 soils	Anionic (-1)	**Kd – 0.804** **Kf – 0.912**	**Y (Kd)** **Y (Kf)**	N	69 (Kd) 65 (Kf)	39 (Kd) 25 (Kf)	Mean Kf,oc
22	5 soils	Neutral	**Kd – 0.966** Kf – 0.57	**Y (Kd)** N (Kf)	N	68 (Kd) 36 (Kf)	15 (Kd) 40 (Kf)	(**Mean Koc**)* Mean Kf,oc
23	4 soils	Cationic (+1)	Kd – 0.000 Kf – 0.41	N	N	51	125	Mean Kf
24	4 soils	Cationic (+1)	**Kd – 0.955** Kf – 0.538	**Y (Kd)** N (Kf)	N	37 (Kd) 80 (Kf)	38 (Kd) 93 (Kf)	(**Mean Koc**)* Mean Kf,oc

Observations

- 8 out of 24 APIs showed correlation with organic carbon (%foc) using Kendall's test and K_F (n = 4) and/or Kd (n = 7)
- These 8 APIs included three of the four APIs with soil-only data
- No correlations were found in the I.D. tool for pH or clay content
- Correlation with cation exchange capacity (CEC) found for 3 APIs

n=4 is the absolute minimum for Kendall's test. It is a non-parametric test which only looks at ranks and inversions. Graphical visualisation is advisable to understand its limitations.

E.g. API 14 correlation of K_F vs %foc:



Pearsons R^2 = 0.59 suggests poor correlation

ID tool Kendall's Test suggests good correlation at 95% significance level (p=0.045)

- Cautious interpretation needed.

Variability

The Input Decision Tool also looks at the variability in the data, using the coefficient of variation (CV)

Based on Kendall's test and CV for K_F/K_{Foc} (or K_D/K_{oc}) the Input Decision tool recommends:

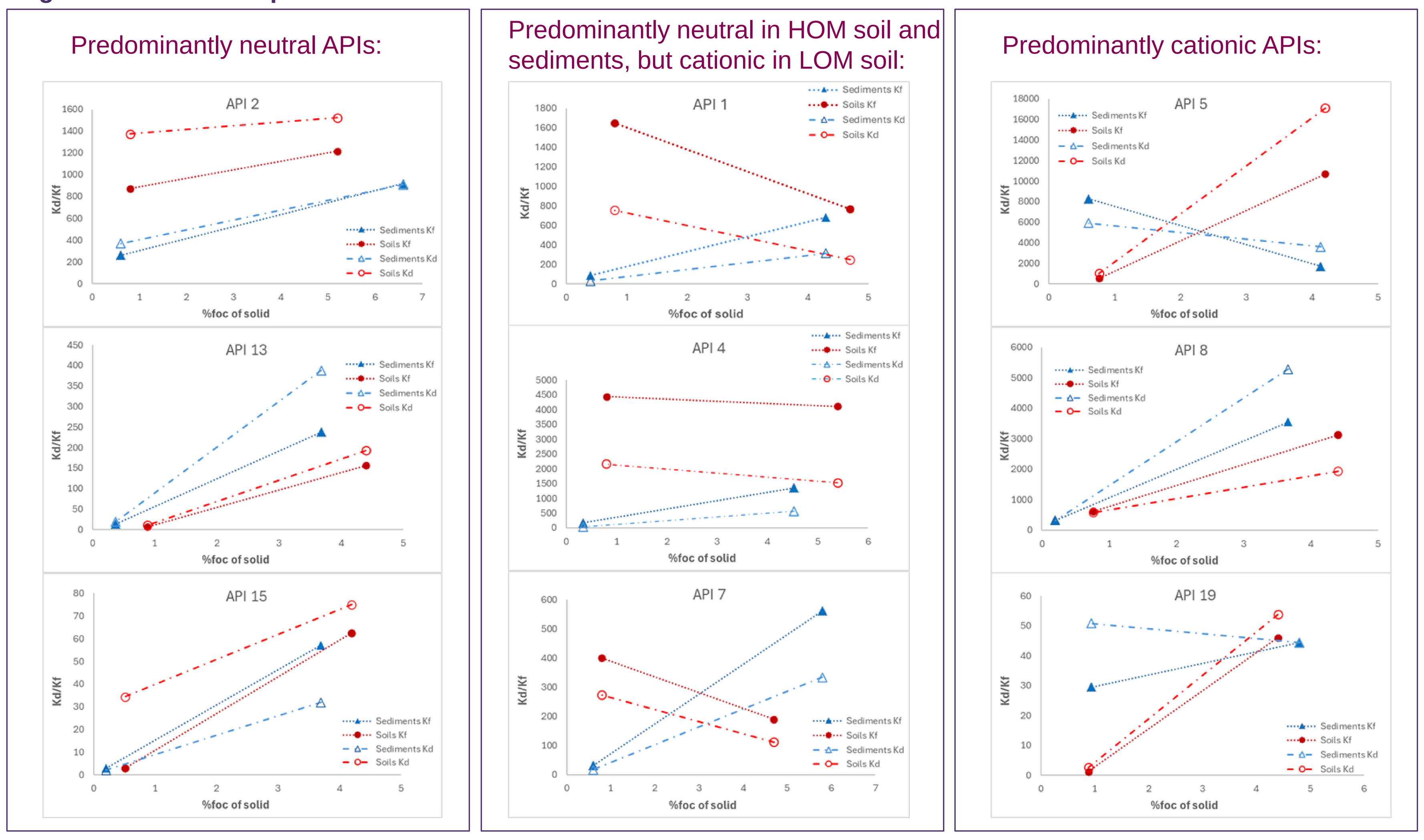
Use the mean K_{Foc} (or K_{oc}) for 11 of the 24 APIs (including the 8 for which Kendall's test identified a correlation with OC)
Rationale: K_{Foc} significant correlation with OC (Kendall's test, p=0.05) and/or CV <60%

Use the mean K_d/K_F for 10 of the 24 APIs
Rationale: Criteria for using mean K_{Foc} not met and K_F CV <100%

Use the 90th %-ile or maximum K_d/K_F for 3 of the 24 APIs
Rationale: Criteria for using mean K_d/K_F not met and K_F CV >100%

Soils vs Sediments

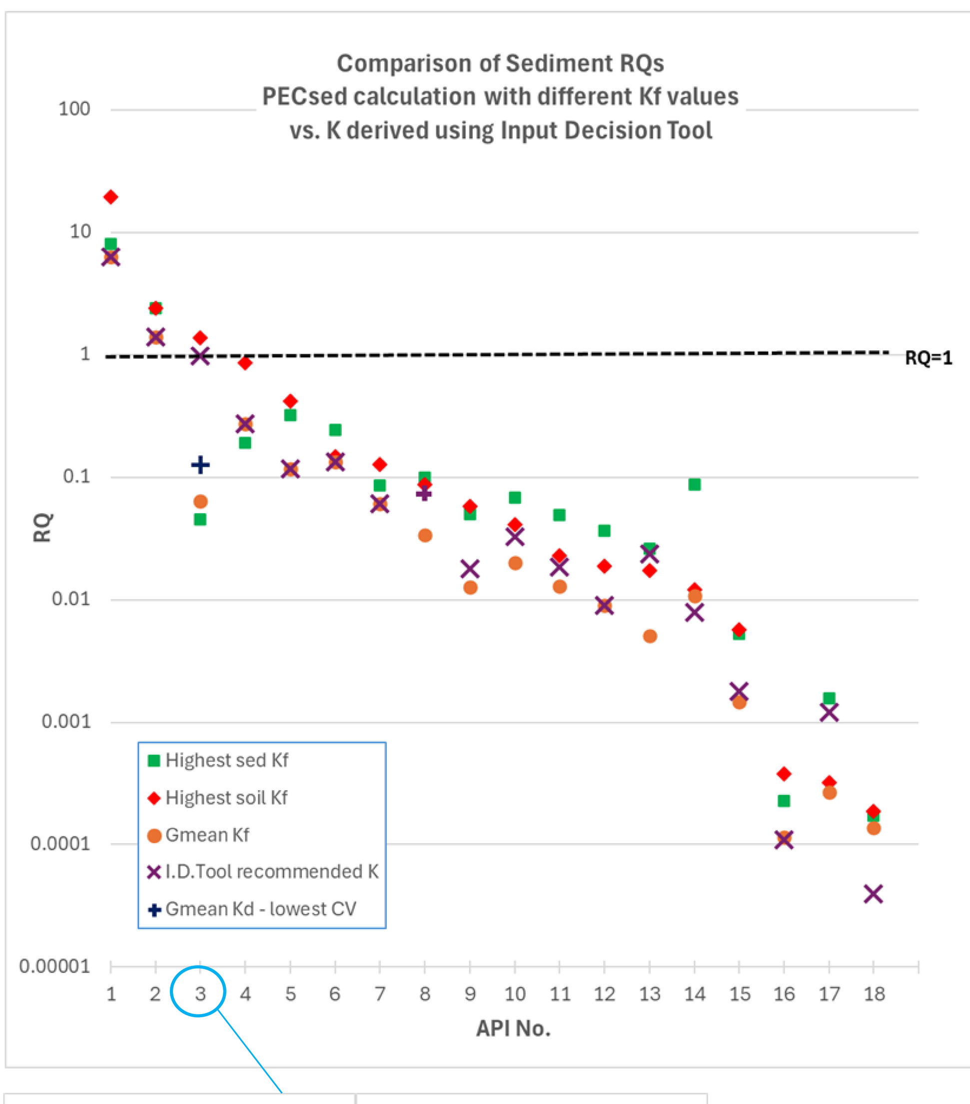
Figure 1: General sorption trends observed

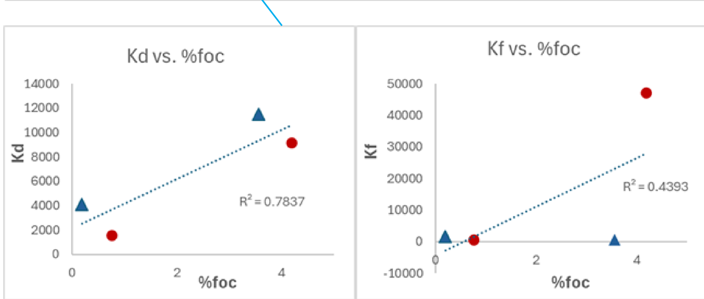


Observations

- 18/24 APIs (75%) showed increased adsorption with higher solid organic carbon content (%foc). These were predominantly neutral or anionic in the experimental pH range (5 – 7)
- Increased sorption with %foc not consistent for cationic APIs; pH influence observed, as well as significant correlations with CEC.

Impact of different assumptions on Risk Quotient (PEC:PNEC ratios) - Sediment Compartment Risk Assessment





Extreme soil K_f value in this example is 20x geometric mean. Suggests closer look at this data is warranted:
- Are Kd's more representative than K_F's ?
- Does sediment data look different to soil ?

Overall, there was no change to the outcome of the sediment compartment risk assessment when using i) sediment K_d/K_F vs. soil K_d/K_F vs. geomean (all solids) or ii) kinetic K_d vs. isotherm K_d/K_F

Conclusions

Calculating geometric mean K_F/K_{Foc} (or K_d/K_{oc}) from pooled soil and sediment adsorption data seems reasonable in most cases, providing CV criteria are met.

- Using soils, sediments or combined soils & sediments made little difference to the sediment risk assessments
- Exceptions when data show high variability in which case the "Input Decision" Tool recommends using the 90%-ile or maximum value

"Input Decision" is a helpful tool for evaluating OECD 106 data and deciding on which K_F/K_{Foc} (or K_d/K_{oc}) value to use in ERA of human APIs under the new EMA Guideline.

- Correlation with other parameters (esp. pH and CEC) needs further investigation.

Correlation with OC (if one exists) is probably more likely to be detected if only soils (or possibly only sediments) are used in the OECD 106 test. If understanding the role of OC is of primary importance, it would be preferable to further investigate:

- Differences in organic matter composition and physico-chemical properties between soils and sediments
- Sorption to different riverine sediments with different composition of organic matter in (e.g.) creak /river and pond/lakes sediments.

References
EMA (2024). Guideline on the environmental risk assessment of medicinal products for human use. 22 August 2024. EMEA/CHMP/SWP/4447/00 Rev. 1- Corr. Committee for Medicinal Products for Human Use (CHMP).
Input-Decision 3.3 Excel-Tool to select input parameters for groundwater simulations. Federal Environmental Agency (UBS) Section IV 1.3 "Plant Protection Products"