Using Systematic Evidence Mapping to Track the Development of Toxicokinetic Models of PFAS From 2000-2021

3120

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Abstract

Pharmacokinetic (PK) models characterize how dose is distributed within the body. In chemical exposure and dose research, PK models are either "classical", generally consisting of one or two mathematically abstract compartments (i.e., central and peripheral), or explicitly physiologically-based (PBPK) with defined tissue volumes. Use of PK models for estimations of per- and polyfluoroalkyl substances (PFAS) in serum have been in use for decades. However, use of models has varied across studies by publication year, location, and referenced papers. This scoping effort seeks to systematically map the current landscape for PFAS PK models, categorizing different trends and similarities across model type, PFAS, and use scenario. A literature review using *Web of Science (WOS)* and the *SWIFT* review tool were used to identify PK models used for PFAS.

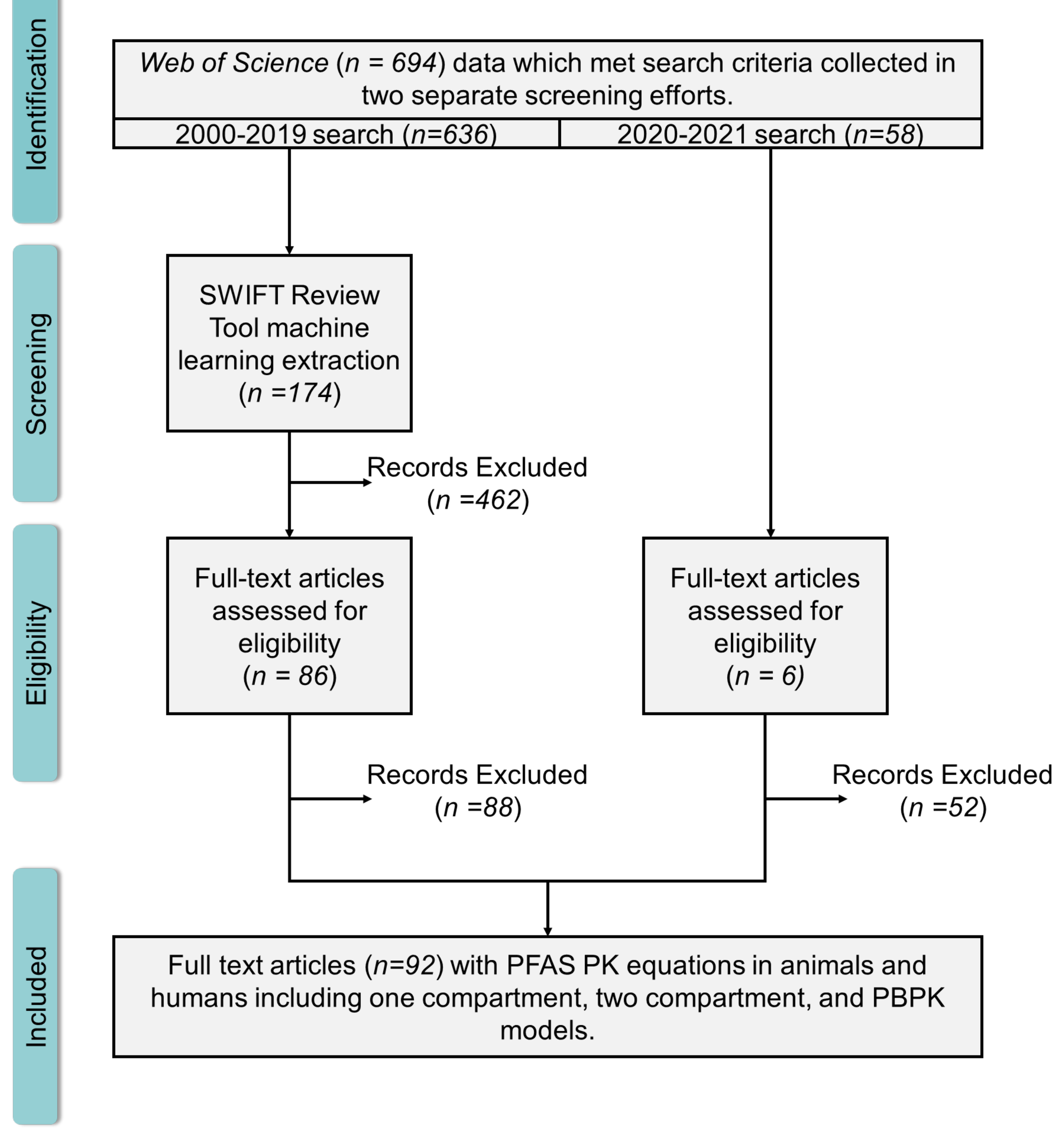
- The assessment covered publications from 2000-2021.
- The most common chemical, PFOA, was included in 69 of the 92 papers, followed by PFOS with 60.
- Within the corpus, 50 papers contained a one-compartment model, 17 two compartment models were found, and 33 used physiologically based pharmacokinetic (PBPK) models.

The scoping assessment suggest that scientific interest has centered around two chemicals – PFOA and PFOS – and most analyses use one-compartment models in human exposure scenarios.

Methods

- Two separate extractions were implemented: one in 2019, and a follow up in 2021 (Figure 1).
- 694 total papers were identified using a *WOS* key string search.
- A 69-paper training set was used to train the *SWIFT* machine learning review tool to extract papers from the 2019 *WOS* library.
- In total, 232 full text articles were manually assessed for eligibility, from which 92 were included.
- Model type, parameters, animal or human, and potential sources were extracted from each article.
- The R Package *Bibliometrix* was implemented to analyze papers for commonalities and visualize trends.

Figure 1. Scoping Assessment Process Flow



Results

Table 1. Chemical by Model Type for Human and Animal Studies

All			
Chemical	One Compartment	Two Compartment	PBPK
PFOA	40	13	22
PFOS	31	8	25
PFHxS	18	5	2
PFNA	12	2	2

Human			
Chemical	One Compartment	Two Compartment	PBPK
PFOA	31	6	13
PFOS	24	4	12
PFHxS	15	1	2
PFNA	11	0	1

Animal			
Chemical	One Compartment	Two Compartment	PBPK
PFOA	9	8	11
PFOS	7	4	15
PFHxS	3	4	1
PFNA	1	2	1

- Among all extracted papers, one compartment models were the most common model type (50), followed by PBPK (33) and two-compartment (17).
- Two-compartment models were employed to model unique scenarios such as mother/child.
- PBPK models were employed to consider mechanisms such as renal resorption. Almost PBPK models were for PFOA and PFOS.
- Seven PFAS were analyzed in 10 or more papers, four of which are included in Table 1: PFOA (69), PFOS (60), PFxS (22), and PFNA (15). Three were not included in Table 1: PFB (13), PFDA (13), and PFHxA (12).

Figure 2. Historiograph of Human One Compartment PK Models used for PFAS (2000-2021)

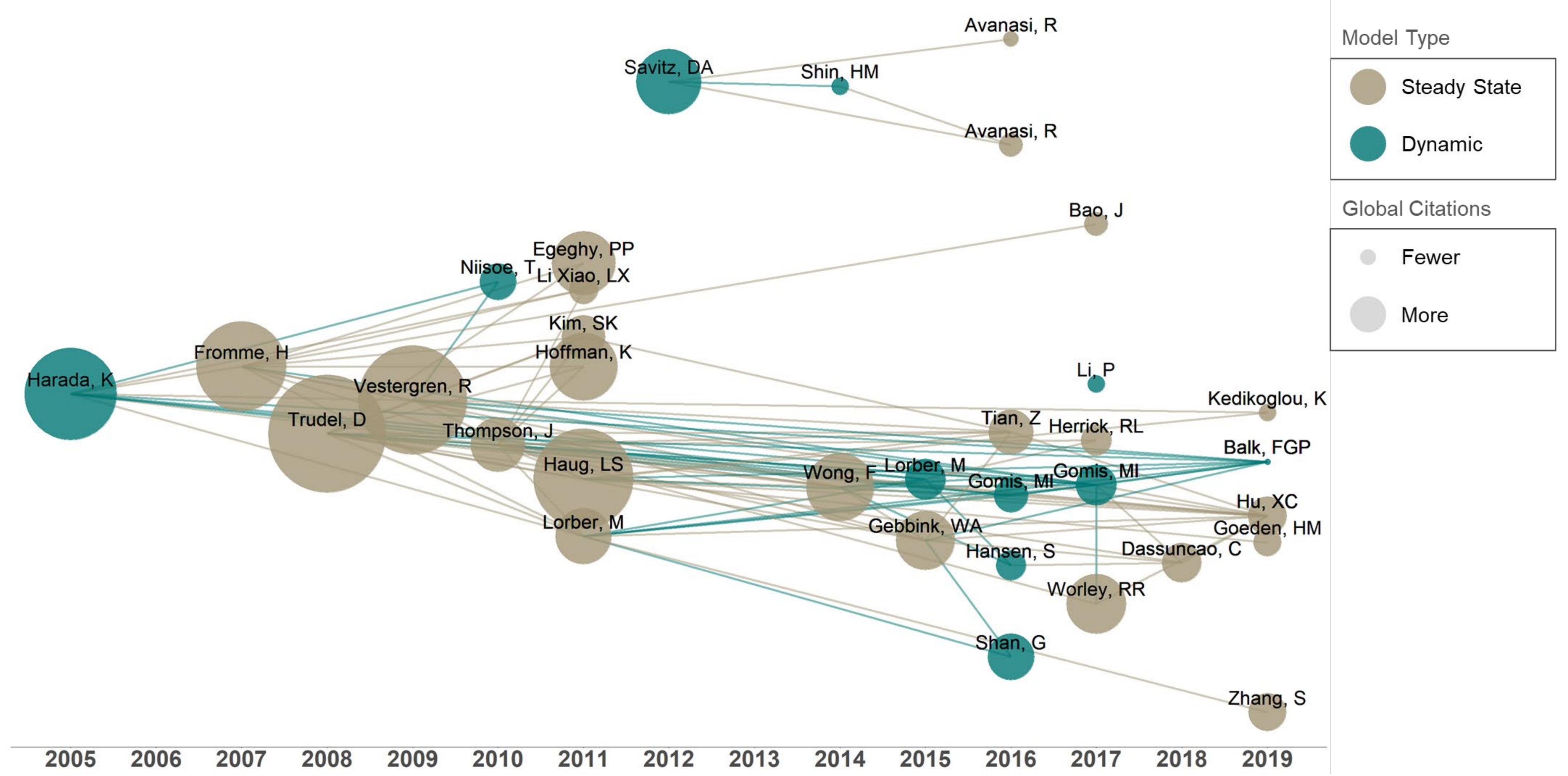


Figure 2: A chronological co-citation network ('historiograph') of papers presenting one-compartment PK models for PFAS in humans (34), produced using the R package *bibliometrix.* Whether a study applied a steady-state or dynamic solution is indicated by color, and the number of global citations is indicated by size. In this review, Harada et al. (2005) was the earliest paper, while Trudel et al. 2008 was the most cited (286) with 15 local references among the 34 total models. The isolated cluster of papers at the top of the figure is a collection on the *C8 Health Project*, an epidemiology study with 69,030 individuals, enrolled over a 13-month period in 2005–2006.

Discussion

PFOA PFOS Focus

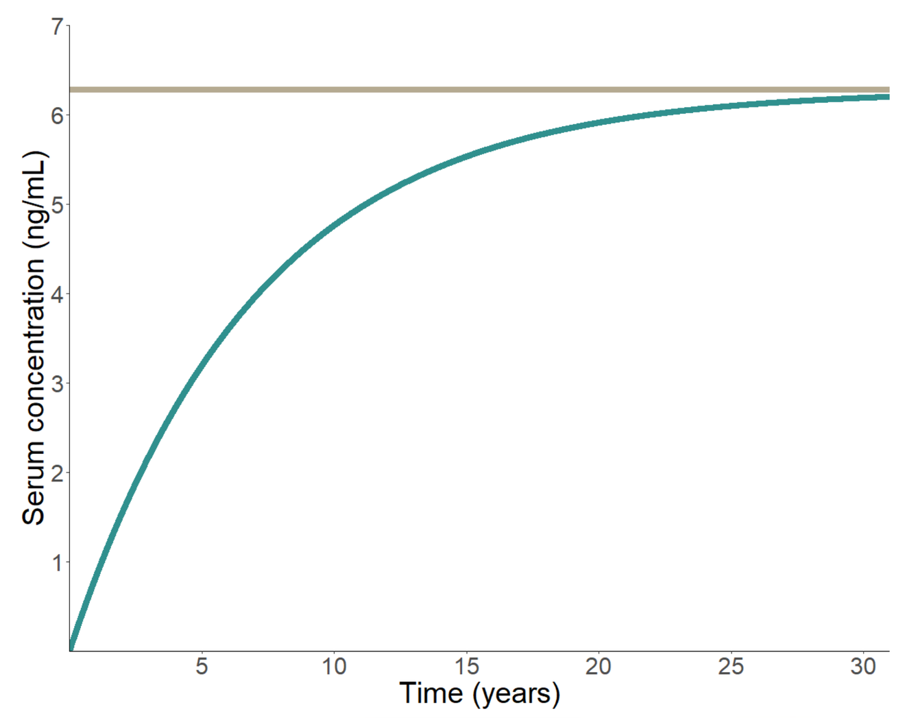
Table 2. 2017-2018 NHANES PFAS Medians and Number of Extracted Papers

Analyte	Median (ng/mL)	PK Model Papers
PFOS	3	69
PFOA	1.4	60
PFHxS	1.1	22
PFNA	0.4	15
PFDA	0.2	13
Me-PFOSA-AcOH	0.1	2
PFUA	0.1	2

PK applications for PFAS have centered on PFOA and PFOS; followed by PFHxS and PFNA. In the 2017-2018 cycle of the Nutritional Health and Examination Survey (*NHANES*), these four analytes returned the largest serum concentrations (ng/mL).

One Compartment Dynamic Model

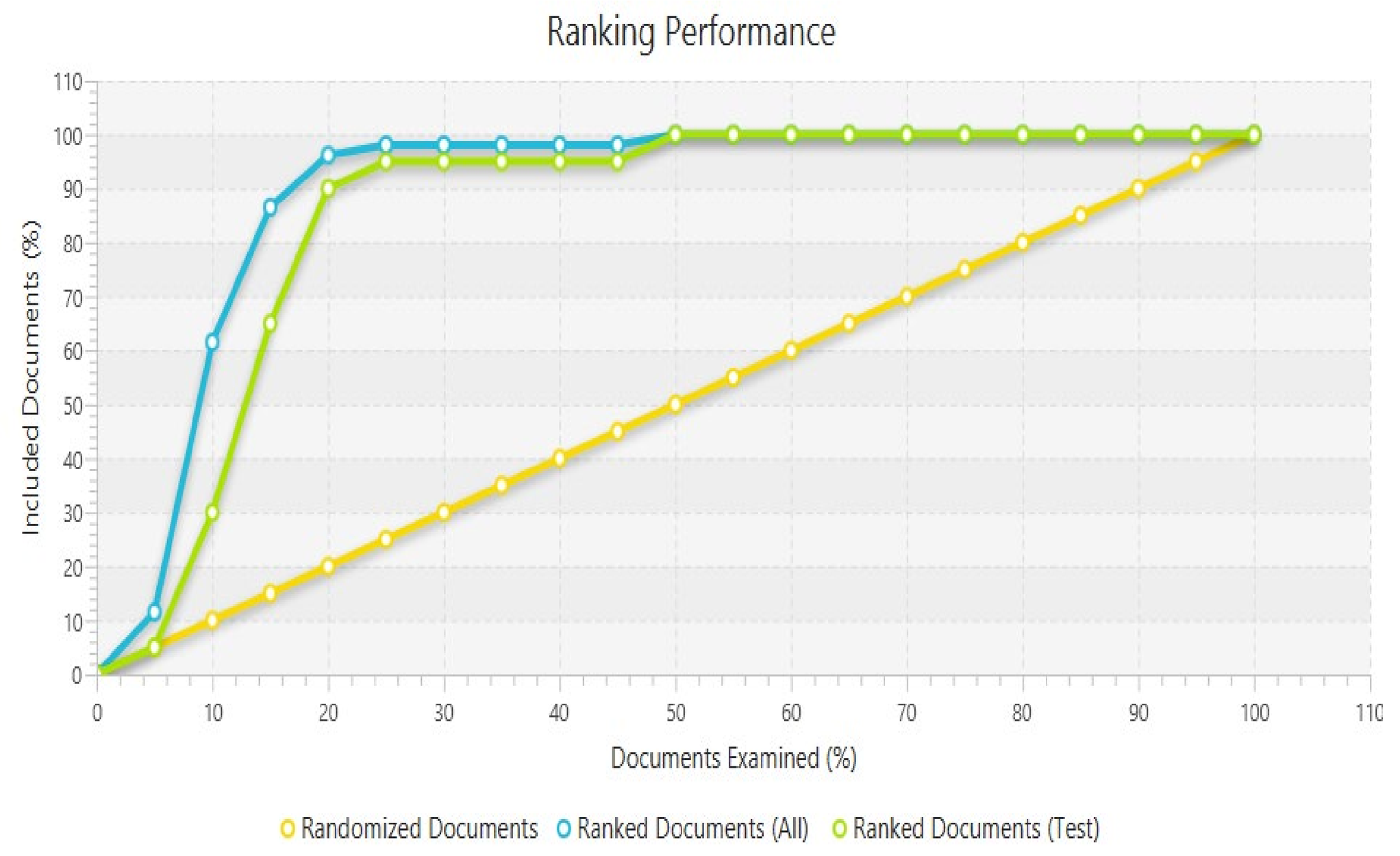
Figure 3. Comparison of Dynamic and Steady State One Compartment Models



- Steady-state models were most the most commonly used (23/34) and cited one compartment model structures (Figure 2).
- For PFAS with long half-lives in humans (e.g., PFOA), steady-state conditions only achieved over long time period (Figure 3, adapted from East et al 2021)
- Steady state models not realistic for some populations (e.g., children, pregnant women).
- Caution should be used when comparing between and drawing inferences from dynamical models and steady-state models

Precision and Recall

Figure 4.Capturing Relevant Documents



- Use of *SWIFT* significantly improved the efficiency of the selection of relevant papers (blue, green lines) compared to a random process (Figure 4)
- Based on application of SWIFT machine learning model to entire corpus(blue) and testing subset (green), restriction of review to about 25% of corpus likely resulted in the exclusion of similar proportions (about 5%) of relevant papers (i.e., recall error)
- However, identified patterns on the estimated ratio of model types (one, two, PBPK) and use (animal/human) are similarly expected across all relevant papers.

Summary

The most common PK models for PFAS are one compartment, steady-state models. More complex models (2-compartment, PBPK) have largely only been applied to PFOA and PFOA. Inferences drawn across studies and models should take model structure into account.