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UNCERTAINTY-INFORMED DEEP NEURAL NETWORK WITH REJECT OPTION: PREDICTING TOXICITY OF PFAS "FOREVER CHEMICALS"

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UNCERTAINTY-INFORMED DEEP TRANSFER LEARNING OF PFAS TOXICITY

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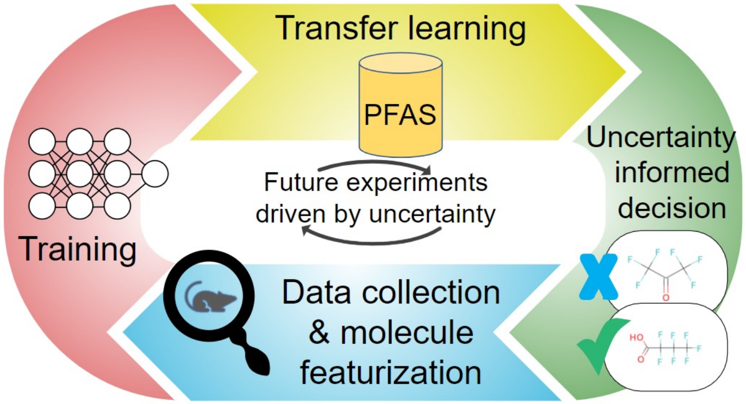


https://doi.org/10.26434/chemrxiv.14397140.v1

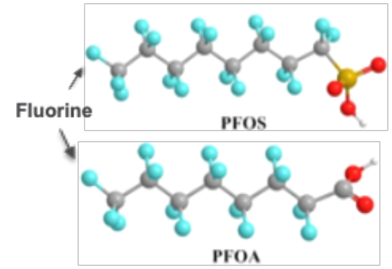
INTRODUCTION & HYPOTHESIS

- **PFAS –** class of man-made chemicals with diverse range of properties and uses. Toxicity properties largely unknown.
- Pose significant hazard for >600 DOE/DOD facilities
- Approaches to assess *in vivo* toxicity are expensive
- Literature demonstrates certain toxicity endpoints may partially be understood and predicted computationally

- **Urgent need to examine the role of computational approaches in aiding or replacing expensive in vivo experiments**
- Can we generally predict PFAS toxicities & uncertainty on EPA list of >8,000 PFAS

PFAS: EMERGING CONTAMINANTS

Per- and polyfluoroalkyl substances (PFAS)



- Class of man-made chemicals of mounting national concern and government attention

Sources and Uses

- **Manufacturing** (uranium processing, metal plating, lubrication)
- **Aqueous firefighting foams** (AFFFs)
- **Consumer/household products**

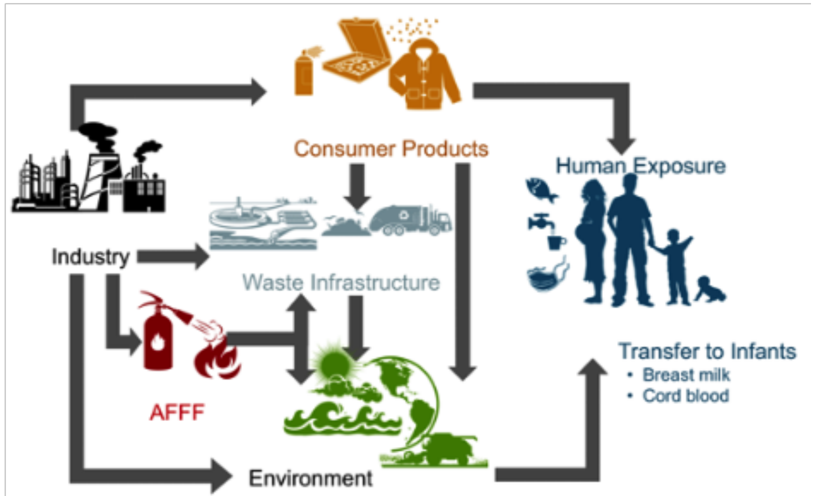
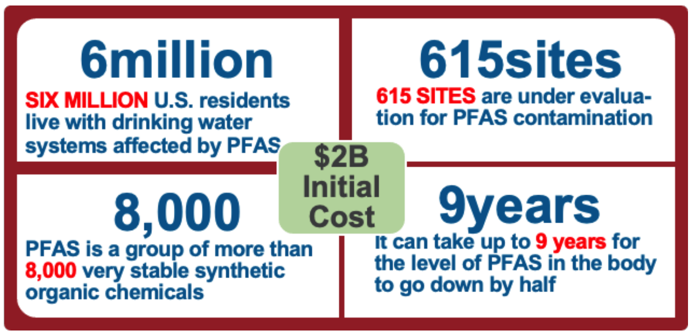
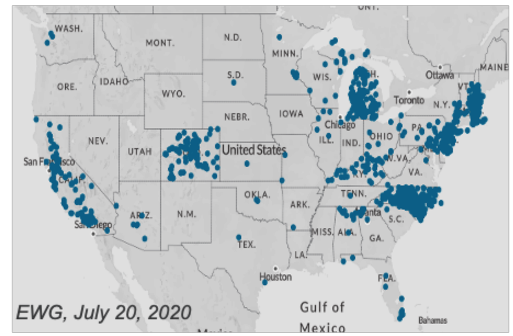


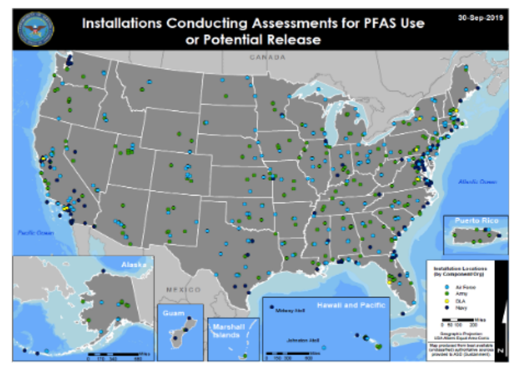
Figure 1 from Sunderland et al. (2019) *Journal of Exposure Science & Environmental Epidemiology 29*(2). doi:10.1038/s41370-018-0094-1

PFAS: ENVIRONMENT & EXPOSURE

Chemical release into environment







Exposure

- **Widespread**
- **Persistent** in environment
- Above advisory levels (not enforced)
- Accumulates in blood, liver, and kidneys when exposed

TOXICITY

- Lifetime Health Advisory for two common PFAS **(PFOS & PFOA)** @ low concentration of PFOS and PFOA **(70 parts per trillion)**
- Understanding of PFAS toxicities lacking across **>8,000** PFAS compounds
- Traditional *in vivo* experiments for toxicity expensive
- Complex due to the range of chemical/biological/cellular factors

TOXICITY

Endpoint

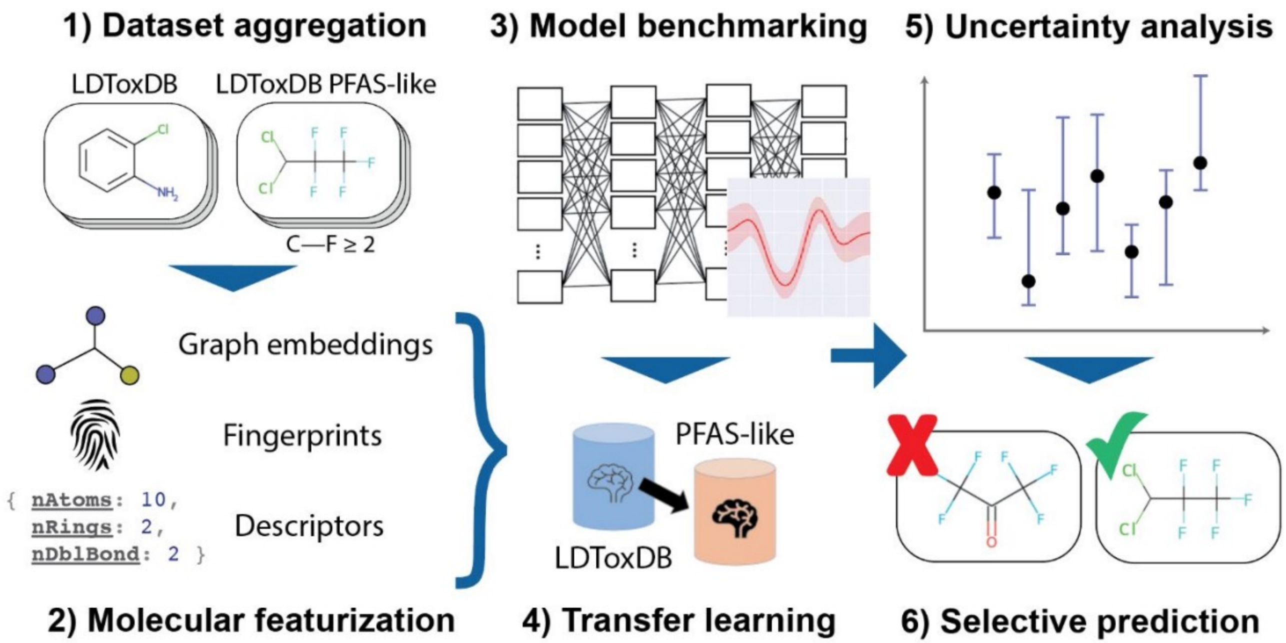
- **Median lethal dosages (LD_{50})** dosage fatal to ½ population of animals
- Measured in substance amount taken orally (g or mol) per lab rat mass
- Units: $^{mg}/_{kg}$ or $-\log(^{mol}/_{kg})$

Category	Toxicity	Dosage (mg/kg)
I	High	≤50
II	Moderate	50 to 500
III	Low	500 to 5,000
IV	Very low	>5,000

EPA toxicity classes

AI4PFAS WORKFLOW

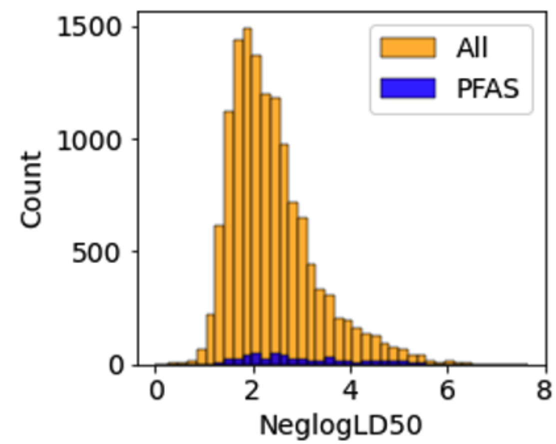
Blueprint for exploration

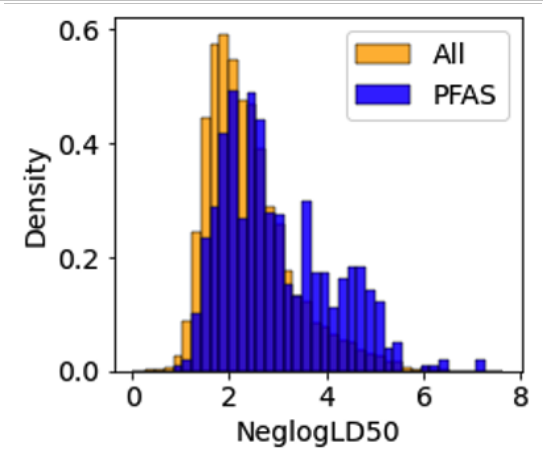


DATASETS

Aggregating toxicity data

- **13,329** organic compounds with oral rat LD_{50} measurements
  - (combined EPA, NIH, NTP datasets) [LDToxDb]
  - **59** PFAS identified by structural (SMILES) match with EPA list
  - **518** (incl. 59 PFAS) selected by quantity of C-F bonds [LDToxDb-PFAS-like]





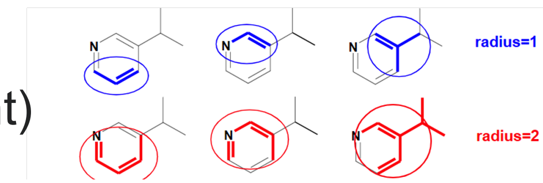
CHEMICAL FEATURIZATION

Calculating molecular descriptors and encodings

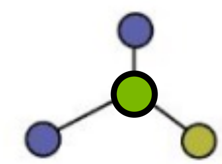
- Molecular descriptors from **Mordred** package

nAtoms	nAromRing	nDblBond
25	0	3
31	2	10
7	0	2

- Fingerprint encodings (**E**xtended-**C**onnectivity **F**ingerprint)



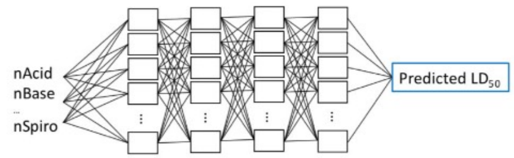
- Graph structure representation (*nodes=atoms, edges=bonds*)



MACHINE LEARNING METHODS

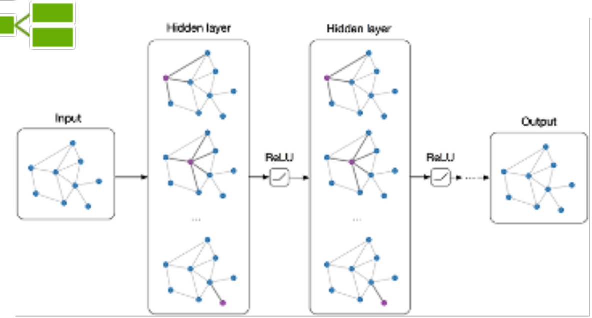
Supervised learning approaches

- Deep neural network (DNN)

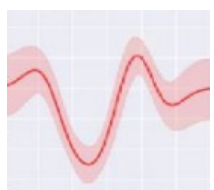


- Random Forest

- Graph convolutional network (GCN)



- Gaussian process



LIT REVIEW + BASELINES

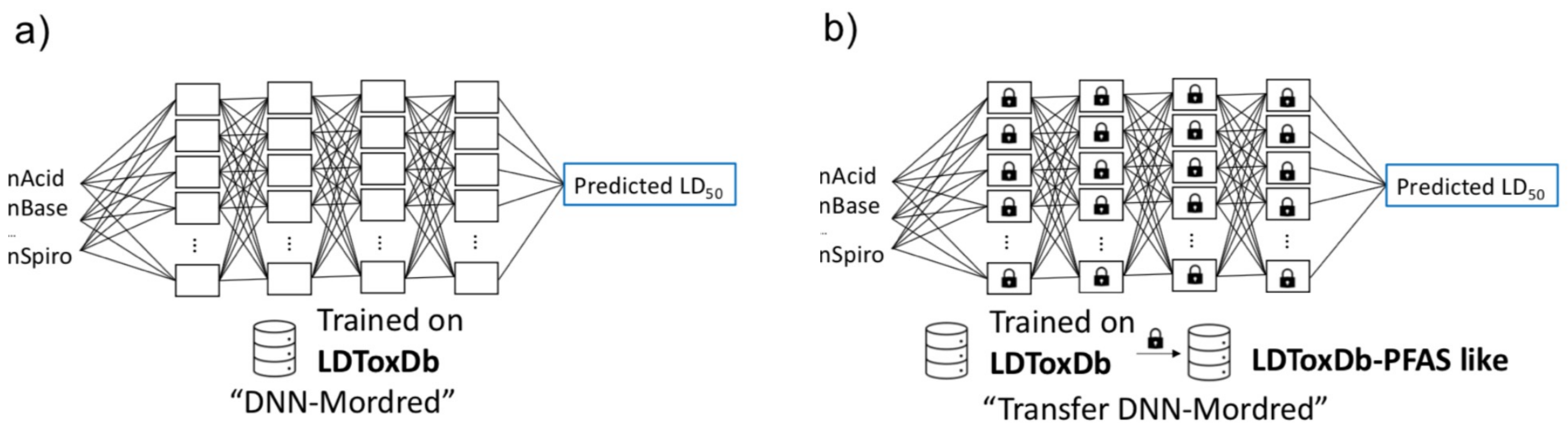
Authors	Year	Dataset	Sample size	Method	R2	MAE	RMSE
Gadaleta et al.	2019	CATMoS	8,448	Ab initio QSAR	0.651	0.39	0.541
Liu et al.	2018	Leadscope Toxicity Db	10,363	RF regressor	0.58		0.60
Wu et al.	2018	EPA ECOTOX	7,413	Consensus (RF, GBDT, ST-DNN, MT-DNN)	0.653	0.421	0.568
Xu et al.	2017	admetSAR, EPA TEST, MDL	12,173	Consensus (GCN)		0.348	0.465
Bhhatarai et al.	2011	ChemIDplus	50 (PFAS only)	Linear regression. Genetic algorithm for feature selection	0.883		0.47
Zhu et al.	2009	ChemIDplus	>8000	Consensus (kNN, RF, hierarchical clustering, NN)	0.71	0.39	

BENCHMARKING MODELS

Method	Input	LDToxDB			
		R^2	MAE	RMSE	Accuracy
DNN	**Mordred descriptors**	0.658	**0.342**	**0.516**	0.680
DNN	2048-bit ECFP, r=1	0.611	0.385	0.549	0.644
GCN	Graph (node=atom, edge=bond)	0.623	0.380	0.541	0.641
GP	10 Mordred descriptors, 200 ECFP bits	0.627	0.376	0.538	0.650
RF regression	Mordred descriptors	0.647	0.372	0.523	0.660
RF regression	4096-bit ECFP, r=2	0.584	0.410	0.569	0.623
RF regression	NMF-reduced 4096-bit ECFP, r=2	0.464	0.479	0.645	0.574

TARGETED LEARNING

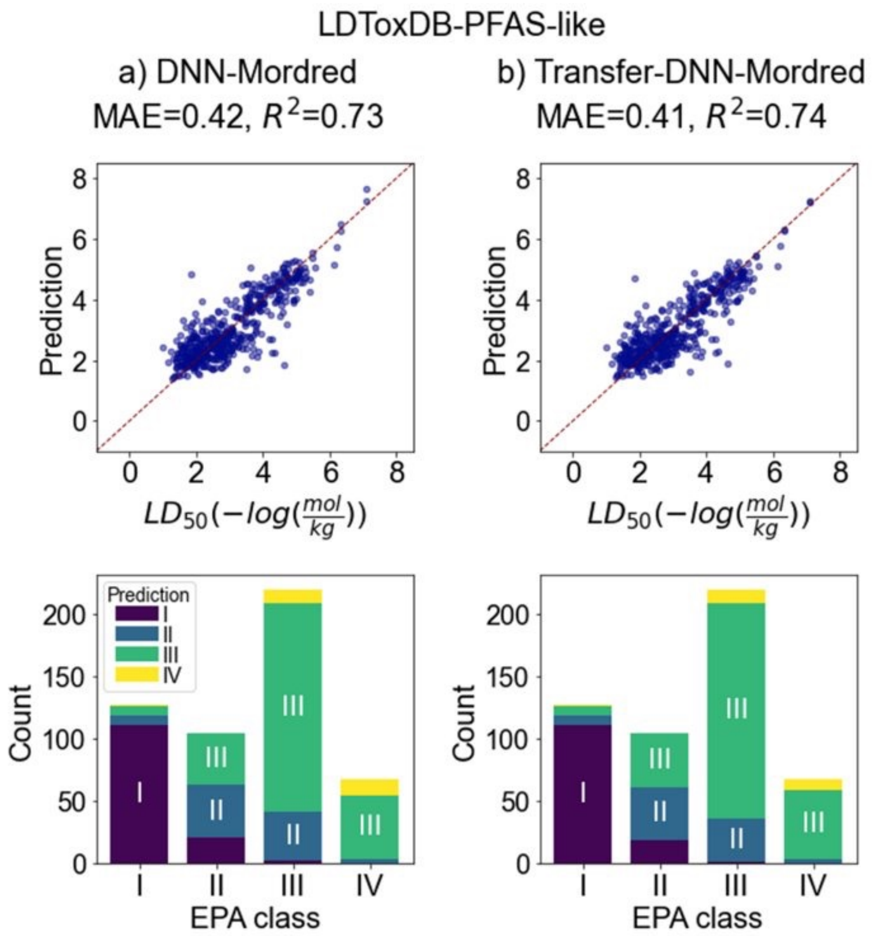
Targeted prediction with transfer learning workflow



TRANSFER LEARNING

Results

- Transfer-step adjustments corresponding with level 1 were used
- No performance degradation
- Positive transfer established



EXPLORING UNCERTAINTY

Approaches

- **Deep ensemble**
  - Multiple DL models trained and converge to different local minima
  - Distribution of predictions made by *N* ensemble models communicates uncertainty

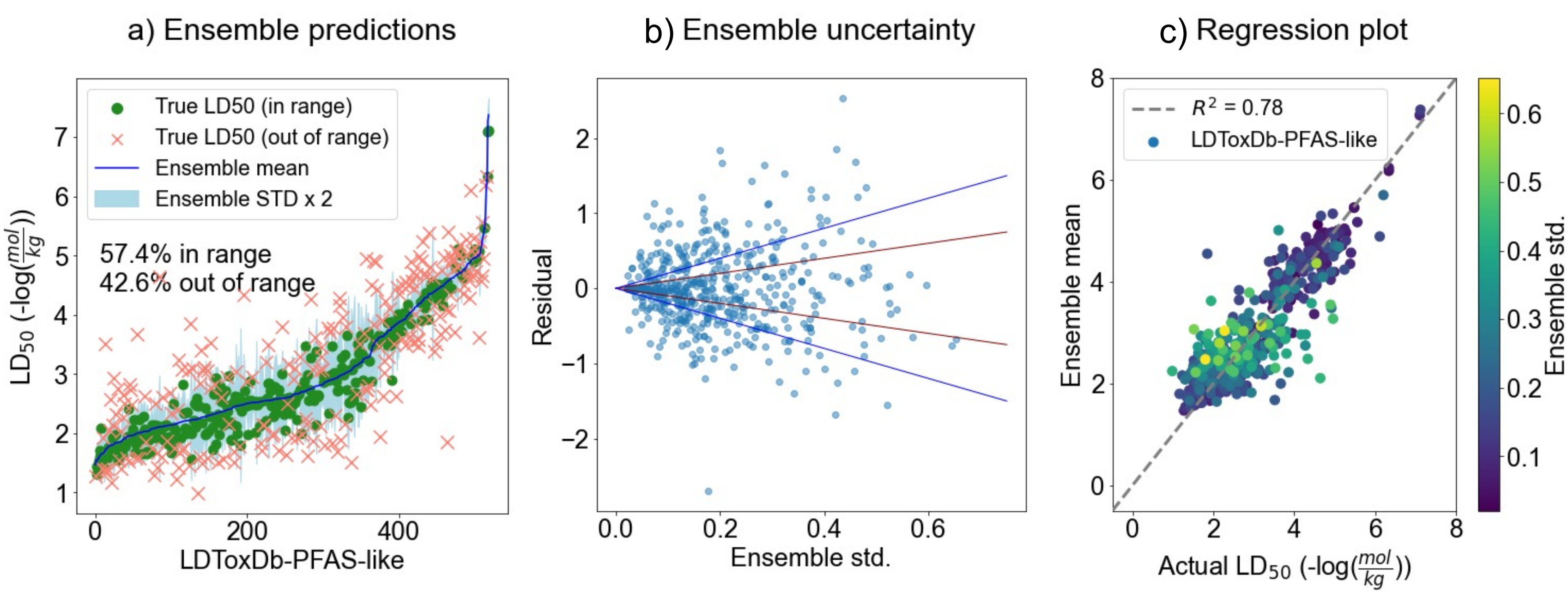
- **Latent space**
  - Dimensional analysis of cross-section of the model's prediction
  - UMAP used on representation layer. *Distance(prediction, training set)* used as correlative metric

Lakshminarayanan et al. Simple and Scalable Predictive Uncertainty Estimation Using Deep Ensembles. *Proceedings of the 31st International Conference on Neural Information Processing Systems* (2017)

Janet et al. A quantitative uncertainty metric controls error in neural network-driven chemical discovery. *Chemical Science* (2019)

UNCERTAINTY ANALYSIS

Uncertainty derived on Transfer-DNN-Mordred predictions



UNCERTAINTY ANALYSIS

Deep ensemble and pitfalls

- Successfully characterization of local uncertainty
- ~58% of uncertainty metrics correspond with prediction error
- Overconfident learning
- Application challenges

SELECTION: TO PREDICT OR NOT TO PREDICT?

Converting uncertainties into automated decisions

- Paradigm which allows the model to respond **"I can't answer", when the confidence is low**

$$(f,g)(x)=\begin{cases} f(x), & if\ g(x) \geq \tau \\ Don't\ know, & Otherwise \end{cases}$$

- Employed within **input space of limited understanding**

Geifman et al. *SelectiveNet: A Deep Neural Network with an Integrated Reject Option.* International Conference on Machine Learning (2019)

SELECTIVE NET: TRAINING

$$\mathcal{L}_{(f,g)} = \underbrace{r(f,g \mid S_k)}_{\text{Selective risk}} + \underbrace{\lambda \max\left(0, \left(c - \phi(g \mid S_k)\right)\right)^2}_{\text{Penalty term for over-abstention}}$$

Selective risk

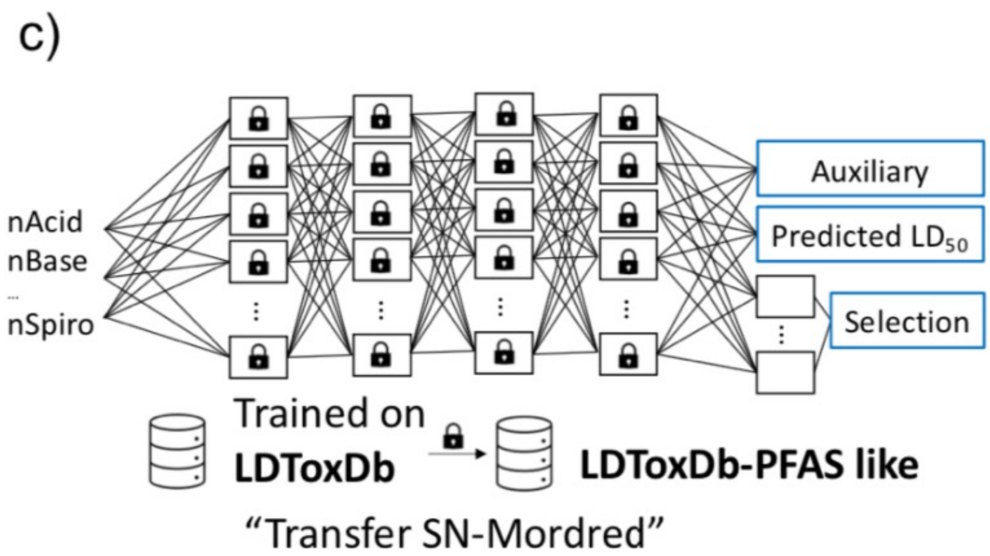
- Abstention comes with no risk
- Prediction carries risk

Penalty term for over-abstention

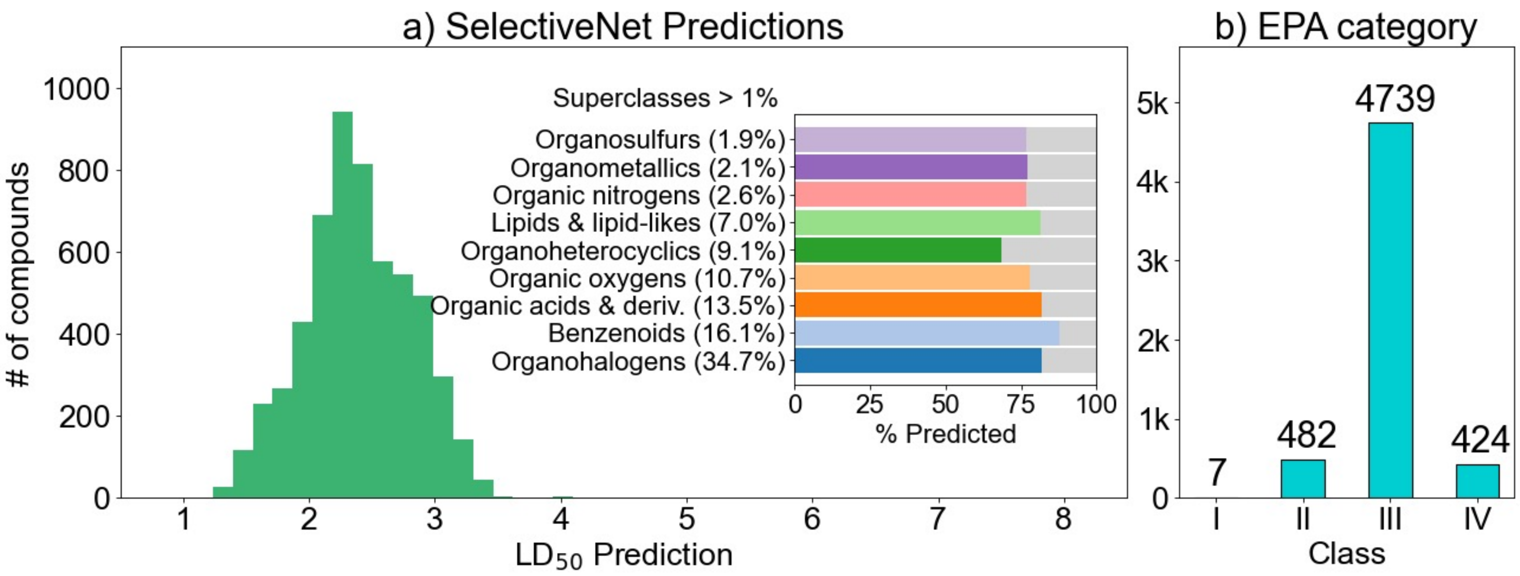
- But may come with penalty
- Comes with no abstention penalty

TRANSFER-SELECTIVE-NET-MORDRED

Predicting EPA list of >8,000



TRANSFER-SELECTIVE-NET-MORDRED

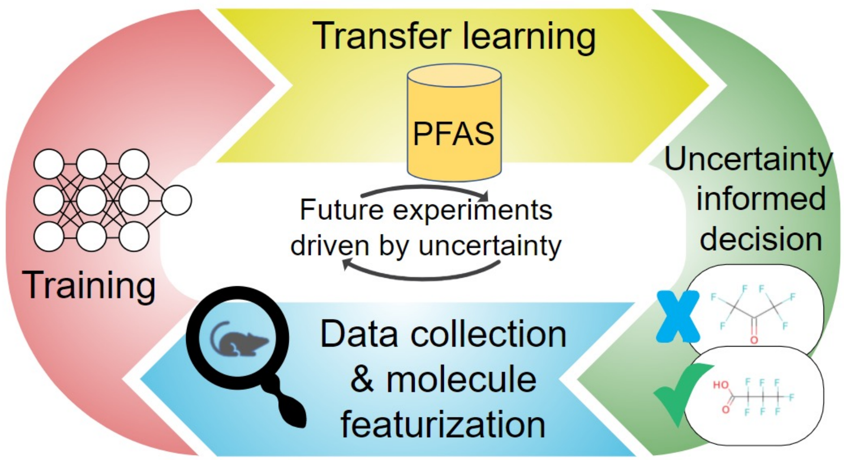


a) Distribution of selective predictions on EPA PFAS structure list. (Inset) Prediction/abstention (%) of ea. superclass. The label provides the % composition of ea. superclass within the entire EPA PFAS structure list.

b) SN-Mordred predictions categorized by EPA toxicity class.

BLUEPRINT FOR COMPOUND SELECTION

Aiding future experimental designs with AI4PFAS



- Active learning
- Computationally-recommended experiments
- Co-informed cycle

- **Paper:** doi.org/10.26434/chemrxiv.14397140.v1
- **Source:** github.com/AI4PFAS/AI4PFAS/

QUESTIONS

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Source: github.com/AI4PFAS/AI4PFAS/

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