



Leveraging Safety Toxicology Data for Enhanced Translatability of Preclinical Adverse Drug Reactions: Insights from the PharmaPendium Tox Navigator

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Introduction

The accurate prediction of human adverse drug reactions (ADRs) from preclinical toxicology experiments remains a significant challenge in drug development, often leading to costly failures in later stages. PharmaPendium's **Tox Navigator** offers a novel approach to improve the translatability of preclinical toxicology findings to human contexts, utilizing regulatory content on marketed and withdrawn drugs. This tool, developed in collaboration with Pfizer facilitate the analysis and investigation of drug candidates' toxicity profiles, is pivotal in addressing drug attrition and predicting human ADRs.

The Tox Navigator compiles and provides access to extensive toxicity data, including regulatory documents and scientific articles covering animal toxicology studies and human safety data. It features tools for quick analysis of drug candidates' profiles, facilitates adverse drug reaction (ADR) investigations across different species, and converts animal doses to human equivalent doses (HED).

This innovative new tool supports the 3Rs by promoting the replacement, reduction, and refinement of animal testing through comprehensive data utilization, efficient study design, and detailed ADR investigations. It also enhances the assessment of patient safety early in the drug development process by providing tools for early identification of safety risks, translational toxicology, regulatory compliance, and better-informed decision-making. These capabilities align with the broader objectives of improving drug safety and efficacy while adhering to ethical standards in research.

Safety Toxicology Data for Enhancing Translatability of ADRs

01 FDA/EMA Safety Data

3 million safety datapoints of marketed drugs with their doses extracted from FDA and EMA regulatory documents.

03 Normalization

Dose value and units were normalized to standard units used in toxicity studies like mg, mg/kg or mg/m²

05 HED

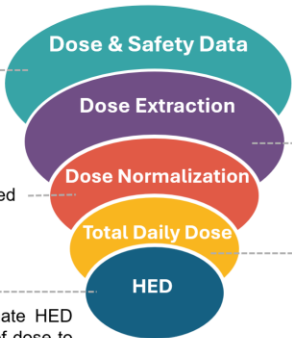
Allometric scaling is used to estimate HED for animal based on normalization of dose to body surface area.

This approach assumes that there are some unique characteristics of anatomical, physiological, and biochemical process among species, and the possible difference in pharmacokinetics/physiological time is accounted by allometric scaling. [1,2]. Thus, HED is determined by Eq. 1 as described in FDA guidance [3,4].

$$HED \left(\frac{mg}{kg} \right) = Animal \ dose \left(\frac{mg}{kg} \right) \times \left(\frac{Animal \ weight \ (kg)}{human \ weight(kg)} \right)^{1-EXP}$$

Eq.(1) : The dose by factor method applies an exponent for body surface area, to convert doses between animals and humans. EXP= 0,67 for small molecules <100kDa and EXP=1 for molecule with a molecular weigh exceeding 100kDa.

Graph (1): Key Differences in Dose Metrics and Human Equivalent Dose (HED) calculations across most used preclinical species and routes of administration allowing allometric scaling based on body surface area using Equation 1.



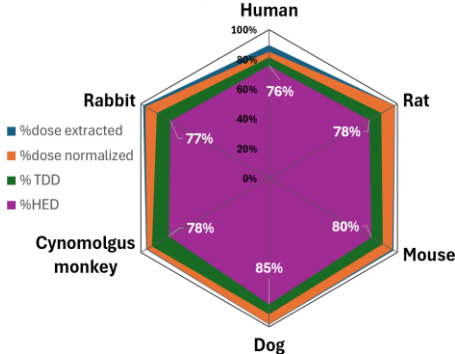
02 Dose Extraction

Doses were extracted automatically from the dose text field and stored in 4 different fields: modulator, low and high dose value, and dose unit.

04 TDD

TDD=dose * frequency
Frequency is how many times per day the drug is administered. When dosing interval exceeds 1 day, the TDD = dose administered
Dose will correspond to the dose value normalized in mg/kg, mg, or mg/m².
If a dose range, only the minimum dose will be used to estimate the TDD.

Main Species HED calculation



Exploring Tox Navigator: Understanding Its Functions and Benefits

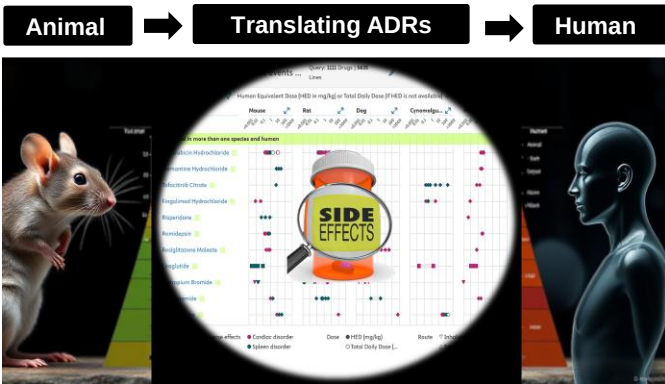
Translational Tox

Navigator: Enables quick analysis of drug candidates' toxicity profiles.

ADR Investigation: Facilitates thorough ADR investigations starting from an overview of ADRs in different species.

Comprehensive Toxicity

Data: Provides detailed toxicity profiles from regulatory documents and scientific articles.



3Rs

Replace



Human Equivalent Dose Calculations
By converting animal doses to HED, the Tox Navigator can help in designing studies that minimize the need for animal testing by providing more accurate assessment of human responses based on existing animal data.

Reduce



Comprehensive Data Utilization
By offering access to extensive toxicity data from previous studies, the Tox Navigator allows researchers to leverage existing data, potentially reducing the need for new animal studies.

Refine



Detailed ADR Investigations
The ability to investigate adverse drug reactions (ADRs) across different species helps in refining study protocols to minimize animal suffering and improve welfare.

Example: Using Tox Navigator to Assess Hepatic Necrosis for Tyrosine Kinase Inhibitors

Tyrosine Kinase Inhibitors

Tyrosine kinase inhibitors (TKIs) have revolutionized cancer treatment, with over 70 approved by the FDA by the end of 2024, targeting 34 primary tyrosine kinases. However, the therapeutic benefits of these agents often come with significant risks, particularly hepatic injury, which remains a common side effect of TKI therapy.

Understanding Hepatic Injury

While our understanding of TKI-induced hepatic injury primarily stems from animal studies and clinical trials, it is crucial to recognize the variability in toxicity profiles. Our innovative Tox Navigator tools provide a streamlined approach to visualize and analyze the risk landscape associated with TKIs.

Hepatic Necrosis in Rodents

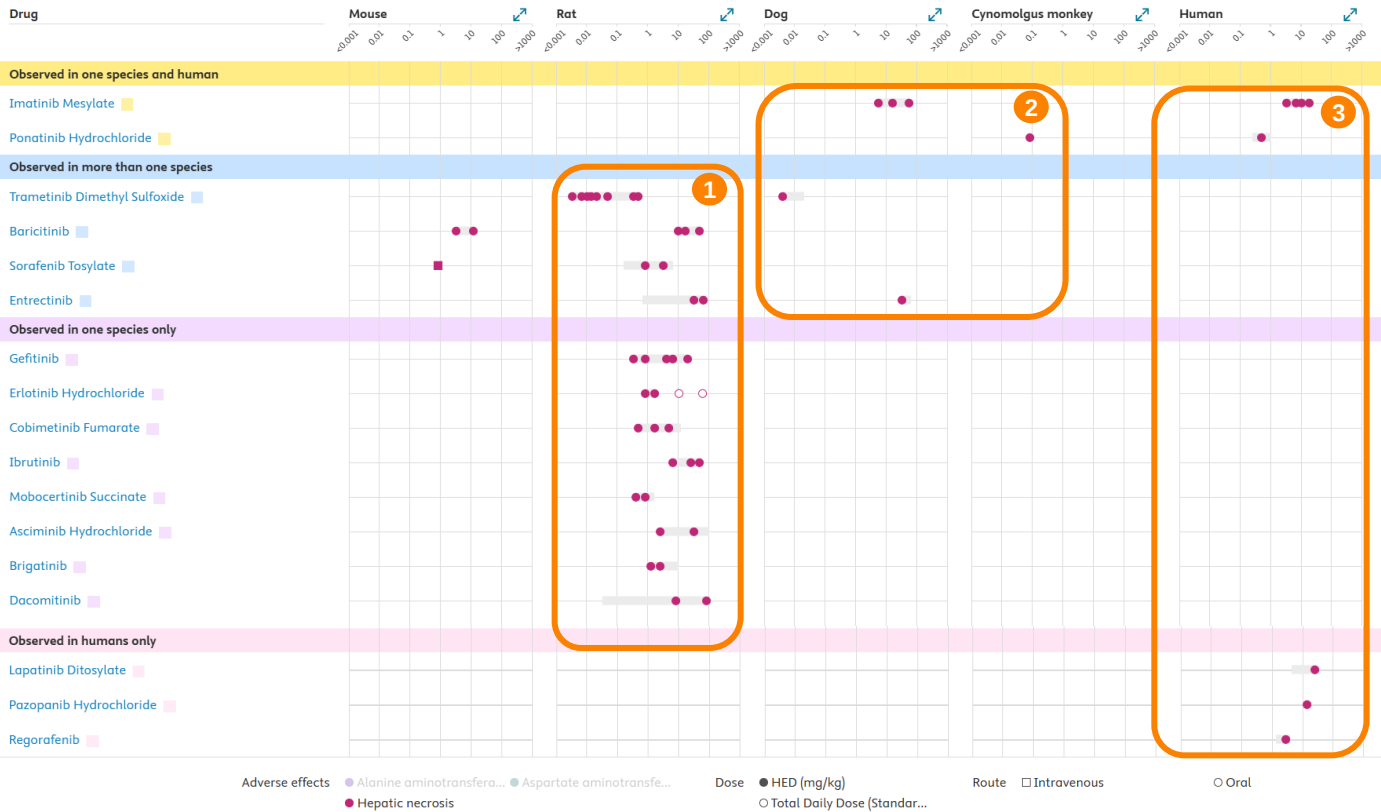
Hepatic Necrosis (HN) has been observed predominantly in rat species, with only a limited incidence reported in mice. Notably, instances of hepatic necrosis associated with TKIs in rats have not successfully translated to human outcomes. This raises important questions about the suitability of the rat model as a reliable proxy for assessing HN in humans. Understanding these discrepancies is crucial for improving the predictive value of preclinical studies and ensuring the safety and efficacy of new therapies.

Hepatic Necrosis in Non-Rodents

HN has been observed in non-rodent species, particularly in dogs; however, the occurrence of HN in rodents does not consistently translate to non-rodent models, and vice versa. This inconsistency complicates the assessment of tumor necrosis across different species. Understanding these variances is essential for refining preclinical models and enhancing our ability to predict hepatic responses in humans, ultimately leading to more effective therapeutic strategies.

Hepatic Necrosis in Human

HN has been reported in humans for only five out of the 72 TKIs currently available in the U.S. market: Imatinib, Ponatinib, Lapatinib, Pazopanib, and Regorafenib. Notably, HN associated with Imatinib and Ponatinib has also been observed in non-rodent species, such as dogs and monkeys, but not in rodent models. In contrast, Lapatinib, Pazopanib, and Regorafenib exhibited no signs of HN in either rodent or non-rodent species prior to their observation in clinical trials. The doses at which HN appeared in humans ranged from 0.5 to 25 mg/kg, aligning with the therapeutic dose for these five TKIs. This highlights the complexities of predicting hepatic toxicity across different species.



References

- [1] Guidance for Industry Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers Center for Drug Evaluation and Research (CDER) July 2005
- [2] Chaturvedi PR, Decker CJ, Odinecs A. Prediction of pharmacokinetic properties using experimental approaches during early drug discovery. Curr Opin Chem Biol 2001;5:452-63.
- [3] Rhomberg LR, Lewandowski TA. Methods for identifying a default cross-species scaling factor. Hum Ecol Risk Assess 2006;12:1094-127.
- [4] Anroop B.N., Shery J. A simple practice guide for dose conversion between animals and human J Basic Clin Pharm. 2016;7(2):27-31

Conclusion

The Tox Navigator supports drug development pipelines by illuminating how early identification of potential ADRs can lead to more informed decision-making, reduced development costs, and ultimately safer drugs entering the market. The Tox Navigator aims to foster a dialogue on integrating advanced data analytics and regulatory insights into preclinical safety assessments, paving the way for more reliable predictions of drug safety in humans.