

# Species Concordance for Liver Injury

## From the Safety Intelligence Program Board

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## Introduction

The Safety Intelligence Program (SIP) is an industry led initiative that harnesses the expertise of its pharmaceutical members, BioWisdom and other key stakeholders to build a comprehensive and high quality intelligence resource for use in the practice of drug safety assessment. SIP strives to ensure that the benefit/risk decisions made for every compound in the development pipeline or drug on the market is based on having visibility to the best information possible.

The 2008 priority for SIP is to focus on hepatotoxicity, in recognition of the challenge in being able to predict, monitor and manage the hepatotoxicity risk associated with new chemical entities approaching approved clinical use. SIP leverages the huge amount of publicly available information to generate an intelligence resource for the safety science communities working in drug development. This intelligence resource is created using BioWisdom's established technology platform (Sofia™) that enables the systematic generation of semantically consistent assertional meta-data. Assertional meta-data comprise relationships between distinct entities, for example, 'Acetaminophen INDUCES Hepatic Necrosis' or 'Bosentan INHIBITS ATP Binding Cassette, Subfamily B, Member 11'. With the capability to reference the original citation, the assertional meta-data can be analysed systematically to reveal new insights related to specific topics.

Here we present a prepublication report that highlights the power of being able to perform systematic and comprehensive analyses on assertional meta-data that captures the current status of knowledge pertaining to a particular area. As an example here, we use an analysis of the degree of concordance of compound-induced effects in the liver between preclinical species and human. We publish this analysis in this form because we believe it contributes part of the necessary evaluation of historic knowledge to advance our collective understanding of drug-induced hepatotoxicity and ultimately lead to an improved capability to assess risk of new chemical entities for liver injury.

## Brief Methodology

BioWisdom's Sofia platform was used to generate assertions that describe the effects of known chemicals in the liver. Vocabularies/thesauri describing >150,000 distinct chemical names and >6000 liver pathologies, physiological processes and clinical chemistry liver biomarkers were used to generate putative assertional meta-data, from publicly accessible information. Specifically, we used Medline abstracts and European Public Assessment Reports (EPARs) published by the European Medicines Agency EMEA. The assertions were passed through a QC process to ensure they accurately reflected (to >97%) the statements made by the authors in the documents. Each assertion was supported by one or more pieces of evidence. Extracted assertions were "semantically normalised" to deal with the inconsistencies inherent in the way authors describe their observations. This process yields a network of inter-related assertions and facilitates the analysis by allowing sets of related observations to be collected together (e.g. all compounds showing cholestatic or biliary effects in rat, or all effects for a set of compounds with chemical similarity).

The analyses of the assertions generated from Medline and the EMEA EPARs were performed separately, since the former represents a significantly larger body of meta-data which may mask the findings in the latter. The EMEA EPARs were especially included because we believe that the

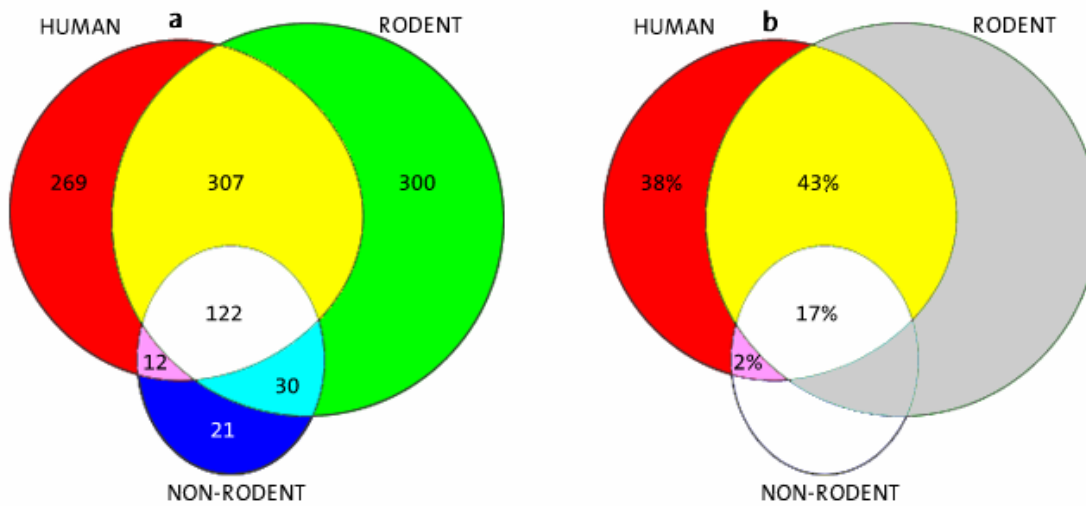
regulatory toxicity data as summarized in these documents represent the most relevant dataset for these types of analysis. The results are presented in separate sections.

With respect to the Medline data, we focussed on those compounds reported to be active ingredients in marketed (or withdrawn) products (1061 compounds). This initial step eliminated non-pharmaceutically relevant compounds from the analysis. Associated with this set of compounds were over 14,600 assertions describing liver effects in a range of species. For the EMEA EPAR data, the analysis indicated a total of 157 compounds to be associated with around 1500 liver assertions.

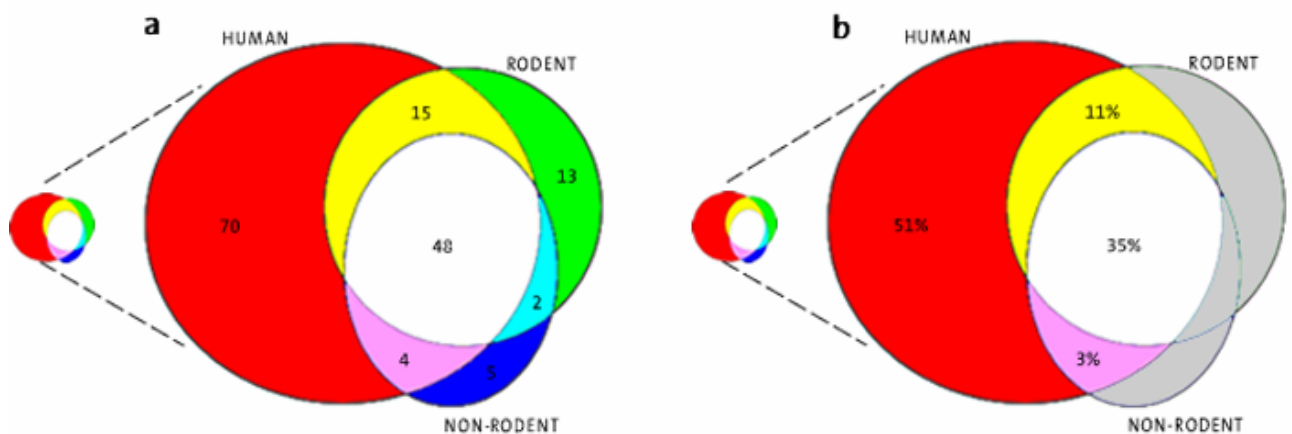
For the compounds identified above, the concordance of assertions between human and non-human species was then examined. The high-level findings are summarised here and presented in the figures below.

## High Level Findings

**Fig 1:** The numbers (a) and proportions (b) of compounds reporting liver effects in humans, rodents and non-rodents, as defined by assertions derived from Medline.



**Fig 2:** The numbers (a) and proportions (b) of compounds reporting liver effects in humans, rodents and non-rodents, as defined by assertions derived from EMEA EPARs. Small venn diagrams indicate the size of the assertional meta-data set relative to that from Medline in Fig 1a and 1b.



## Summary of Analysis

With respect to the prediction of hepatotoxicity in humans, the analysis summarised in Figure 1a and b and Figure 2a and b reveals the following:

- **Compounds showing liver effects in humans:**
  - Medline: 710 out of 1061 compounds (Fig 1a).
  - EMEA: 137 out of 157 compounds (Fig 2a).
- **Prediction of human liver effects by rodents and non-rodents.** Compounds showing effects in humans but with no reported effects in rodents or non-rodents, i.e. the potential “false negative” rate:
  - Medline: 269 out of 710, i.e. 38% of the compounds (Fig 1a and 1b).
  - EMEA: 70 out of 137, i.e. 51% of the compounds (Fig 2a and 2b).Although findings vary somewhat, both data sets are supportive of the notion that human liver toxicity can not always be reliably predicted by preclinical animal species.
- **Concordance between human and rodent findings.** Comparison of human and rodent liver effects in Medline- and EMEA-derived assertions showed that 60% and 46% of compounds respectively produced effects in both humans and rodents (Fig 1b; 43+17% and Fig 2b; 11+35%).
- **Concordance between human and non-rodents findings.** The concordance of compounds inducing human and non-rodent liver effects is lower than that observed for humans and rodents. Thus there was 19% (Fig 1b; 17+2%) and 38% (Fig 2b; 35+3%) concordance respectively in the Medline and EMEA datasets. Especially for the Medline dataset, we believe that this is likely biased by the paucity of published non-rodent data and/or a skewing towards the use of using rodents for testing. The fact that the human/non-rodent concordance is higher for the EMEA dataset reflects the regulatory requirement for non-rodent studies.
- **Compounds with effects in humans that also show effects in non-rodents but NOT in rodents.** In the Medline-derived assertions, this represented 2% (12) of those compounds showing liver effects in humans (Fig 1a and 1b). For the EMEA dataset, this was 3% (4) of the compounds (Fig 2a and 2b). Although one has to keep in mind the caveat mentioned above, relating to the possible paucity of reported non-rodent data especially in Medline, this would indicate that non-rodent data add little to the overall concordance to human.
- **Prediction of compounds with effects in humans on combined findings in rodents and non-rodents.** By combining non-rodent with rodent data, the prediction of compounds that would have liver effects in humans would not increase dramatically, i.e. changing from 60 to 62% (Fig 1b) in the Medline-derived assertions and from 46 to 49% in the EMEA-derived assertions (Fig 2b).
- **Compounds with effects in non-humans ONLY.** The number of compounds that show liver effects in non-human species only is 351 out of 1061 (33%) in the Medline and 20 out of 157 (13%) in the EMEA dataset. This either reflects compounds having no real effect in humans, or compounds for which human development was pre-emptively discontinued or risk mitigated e.g. by dose adjustments. The lower percentage found in the EMEA-derived assertions may also be explained by the more complete and rigorously assessed (clinical and non-clinical) data available in these cases. Especially regarding the Medline dataset, the systematic nature of the assertion generation within the Safety Intelligence Program allows us to assume “absence of evidence” as a surrogate of “evidence of absence” and, hence, these findings could represent “false positives” in the use of non-rodent studies to predict human liver injury. While we accept that, for a number of these compounds, there may

actually be unreported cases of human liver effects, it is unlikely that this will be true in all cases. Regarding the EMEA-derived assertions, given the regulatory requirements, the absence of findings may be regarded with much more confidence as “evidence of absence”. This would, dependent on the dataset, indicate a “false positive” rate of anything between 13 and 33% in predicting human liver injury.

### Caveats

This analysis does not take into account assertions that state that a compound DOES NOT induce a particular liver effect. Evidence for such assertions from both Medline and the EMEA EPARs was collected, but was reported relatively infrequently and was therefore excluded from the analysis. Consequently, the bias that is likely inherent in the published literature, as well as the possible paucity of non-rodent data highlighted above, may influence the results and our interpretation, especially regarding the Medline-derived assertions.

## Overall Conclusions

The work cited in this report demonstrates the technical feasibility of rendering the wealth of historic information available publicly into a semantically consistent format which can be readily utilized to derive an objective and contemporary understanding of the relationship between various drug-induced liver effects across different species.

The analysis shows that between 38 and 51% of compound-induced liver effects reported in humans are not detected in non-clinical test species. Also, in 13 to 33% of the cases, evidence of liver effects in non-clinical test species is not reflected in humans. Moreover, the general comparison in findings between the Medline- and EMEA-derived assertions indicates that non-rodent species are not significantly more relevant than rodent species in predicting human liver effects.

## Future Studies

Future studies relevant to the prediction of human liver toxicity by preclinical studies being performed by the SIP Board include the following:

- Further segregation by different species (cat, dog, rat, mouse, monkey, sheep).
- A correlation of groups of distinct liver effects across species, in order to assess whether any particular liver pathology is more predictive across species than another.