KP207

Toxicity Evaluation System for Chemical Compounds Based on Bayesian Net

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1. Introduction

The evaluation and prediction of the RDT (repeated dose toxicity) of chemical compounds is an important issue. We need a comprehensive evaluation system using the results of similar compounds, their physical properties as well as knowledge on metabolism and toxicity mechanisms. Bayesian net is a well-known framework when the probabilistic inference is important [1]. We propose a prototype system using Bayesian net that enables the evaluation of blood and liver toxicities by aromatic amines. A toxicologist can use the system in order to predict the toxicity of new chemicals and the interpretation of experimental results.

2. Method

Figure 1 shows a metabolic transformation scheme of aromatic amines and their relationship to blood and liver toxicities [2]. We constructed a Bayesian net with this topology, and initialized its CPT (conditional probability table) values subjectively. Three hypothetical compounds (toxic to blood and liver, toxic to blood only, and no toxicity) are assumed. Repeated application of the sensitivity analysis has enabled the refinement of CPT values, and we could get a net that explain the toxicity of these 3 compounds.

The next method used is the conflict analysis in Bayesian net. Let us suppose a simple sequential net shown in Figure 2. An evidence set: (A=T, C=T) is reasonable and we call it a convincing path. On the other hand, if we set an evidence set (A=T, C=F), the resulting likelihood value is very low suggesting the occurrence of a conflict in the evidences or in the net.

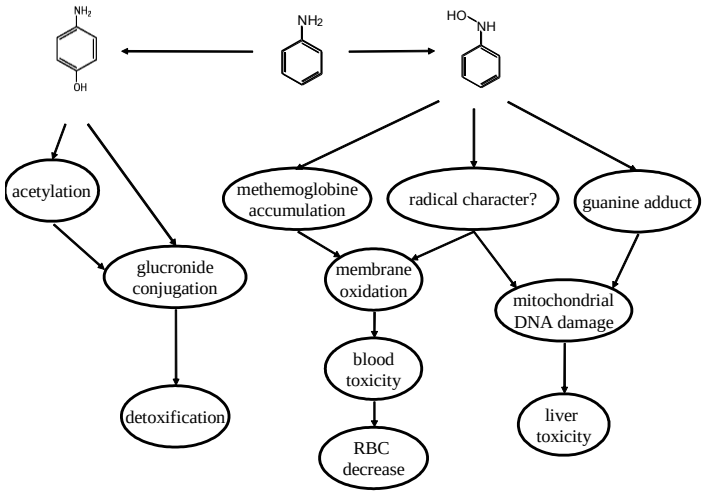

Fig.1 Toxicity Mechanism of Aromatic Amines

3. Results and Discussion

We used rat RDT data of 14 aromatic amines collected at NITE. Probabilistic inference to these compounds resulted in conflicts between the liver and blood toxicities for 5 compounds, and the trials of changing CPT values could not solve them.

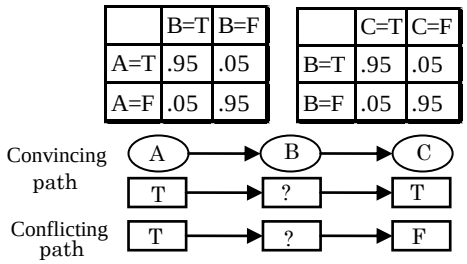

Fig.2 Conflict Analysis

Suggestion by a toxicologist was the incorporation of a factor affecting the metabolite distribution between blood and liver, and we included a node of *logP* value for the N-oxidized compounds (shown by a double circle in Figure 3). CPT values were adjusted so that minimal number of conflicts appeared from the given evidences.

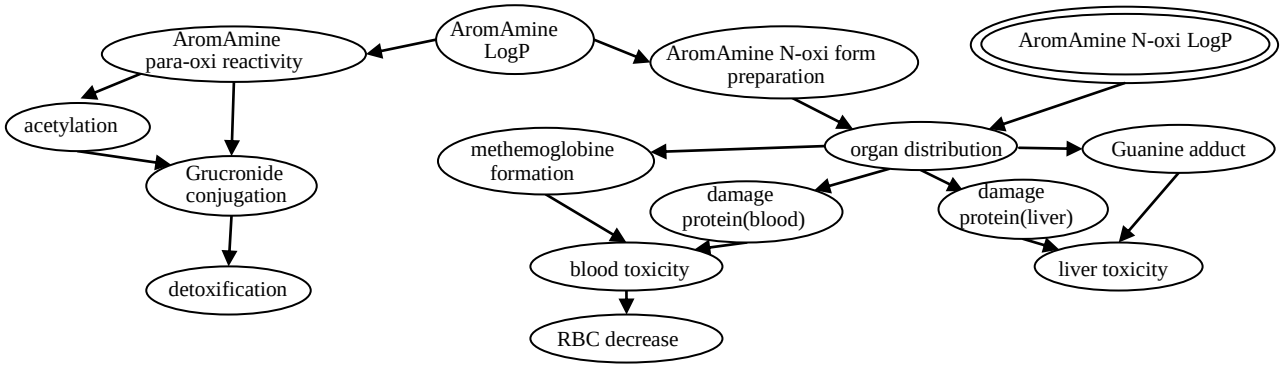

Fig.3 Bayesian Net of Blood and Liver Toxicities by Aromatic Amines.

The resulting CPT values show that (1) a high *logP* of a raw compound led to some kind of toxicity, (2) the *logP* value of the N-oxidized one decided its distribution in organs (high: liver and blood; medium: blood; low: others). It explains the toxicity of 12 compounds, and 2 conflicting compounds are shown in Table 1, suggesting the necessity of some new mechanism.

The collaboration of toxicologists and probabilistic inference has enabled the construction of a reasonable Bayesian net and has inspired the generation of a new hypothesis. We are going to extend the net to include other endpoints and groups of compounds. Automatic refinements of CPT values as well as a GUI system to show convincing/conflicting paths are also in progress.

Table 1. Compounds with Conflicts

Compound	*LogP*		Blood toxicit	Liver toxicity
	raw	N-oxidized		
3,4-Dimethylaniline	2.21	2.13	low	high
1-amino-3-nitro benzene	1.01	0.96	high	high

References

1. Kjaerulff UB, Madsen AL. “Bayesian Networks and Influence Diagrams: A Guide to Construction and Analysis” Springer (2007).
2. Klaassen CD. “Casarett & Doull’s Toxicology 6th ed.” McGraw-Hill (2004).