Validation of Repeated Dose Toxicity Categories of HESS profiler using COSMOS and ToxRef data

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Introduction

Hazard Evaluation Support System Integrated Platform (HESS) [1] and OECD (Q)SAR Toolbox [2] are two compatible hazard evaluation platforms used for predicting repeated dose toxicity of chemicals based on the category approach. The HESS system was developed by National project of Japan, and released free of charge from the following NITE's website in June 2012.

http://www.safe.nite.go.jp/english/kasinn/qsar/hess-e.html

HESS system includes a database with repeated dose toxicity data for about 500 chemicals obtained under Japanese Chemical Substances Control Law (CSCL), and toxicity mechanism knowledge database collected from scientific journals. The HESS system includes a collection of 34 toxicological categories organized as repeated dose toxicity (RDT) profiler (Table 1). Each category is defined based on known toxicity mechanisms and related toxicological effects for 28 chemicals classes extracted from the repeated dose database. The RDT profiler is used for toxicological assessment, grouping chemicals in categories and filling data gaps.

External validation of RDT categories is an important process for improving the reliability and the predictability of the categories. Preparation of an external validation set with enough repeated dose toxicity data by using Japanese CSCL sources was very difficult. In this respect, we have used toxicity data from other two projects COSMOS [3] and ToxCast [4] in order to provide with a considerable number of reliable data. In this presentation, we have reported the result of an external validation of the RDT categories in the HESS profiler by using data of HESS (general industrial chemicals), COSMOS DB (cosmetics ingredients etc.) and ToxRef DB (pesticide etc.)

1. Sakuratani, Y. Zhang, H. Q.; Nishikawa, S.; Yamazaki, K.; Yamada, T.; Yamada, J.; Gerova, K.; Chankov, G.; Mekenyan, O.; Hayashi, M SAR QSAR Environ. Res. 24, 2013. 617-629.
2. http://www.qsartoolbox.org/
3. http://www.cosmostox.eu/home/welcome/
4. http://www.epa.gov/ncct/toxcast/data.html

Method

The set of 638 chemicals different than the chemicals in the local training sets associated with the toxicological categories were used as the validation set. The chemicals are supported with repeated dose data having similar test condition as those of the training set.

Results and Discussion

The HESS profiler categorized 16% of the chemicals within the validation set and for most of them (77%) toxicological effects related to their category were observed in their repeated dose toxicity test (Table 2).

Based on the result of a categorization by HESS, read-acorss can be conducted by an expert. Figure 2 shows a graphical plot of LOEL predicted by read-across based HESS category against observed LOEL for target effect. As can be seen most predicted effects that have LOEL less than 300 mg/kg/day have observed LOEL less than 300 mg/kg/day.

In summary, the validation study demonstrate that the read-across by using HESS is applicable for predicting primal effect of untested chemical at least screening level. The predictivity of HESS categories can be improved by clarifying the definition of the categories based on the structural features of chemicals. In the near future, we are going to improve the domain of the HESS profiler by developing new categories based on unclassified chemicals.

Acknowledgements

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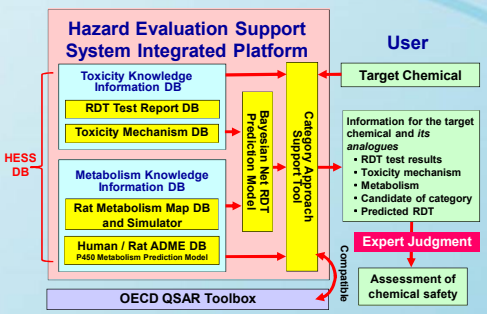

Fig.1 Structure of HESS

Table 1. RDT categories in HESS

	Structure	Toxicity	# of Chemicals in Trainning Set
1	4,4'-Methylenedianilines/Benzidines	Hepatobiliary toxicity	5 (5)
2	Acrylamides	Neurotoxicity	2 (2)
3	Aliphatic amines	Mucous membrane irritation	5 (5)
4	Aliphatic nitriles	Hepatotoxicity	4 (6)
5	Aliphatic/Alicyclic hydrocarbons	Alpha 2u-globulin nephropathy	6 (6)
6	Anilines	Hemolytic anemia with methemoglobinanemia	18 (19)
7	Anilines	Hepato toxicity	18 (19)
8	Aromatic Hydrocarbons	Liver Enzyme induction	9 (9)
9	Azobenzenes	Hemolytic anemia with methemoglobinanemia	2 (2)
10	Benzene/Naphthalene sulfonic acid	Less susceptible	13 (13)
11	Benznesulfonamides	Toxicity to Urinary System	2 (3)
12	Diphenyl Disulphides	Hemolytic anemia with methemoglobinanemia	1 (1)
13	Ethyleneglycol Alkylethers	Hemolytic anemia	5 (5)
14	Ethyleneglycol Alkylethers	Testicular toxicity	2 (2)
15	Halobenzenes	Hepato toxicity	10 (10)
16	Halobenzenes	Renal toxicity	10 (10)
17	Halogenated Aliphatic Compounds	Hepato toxicity	17 (20)
18	Hydrazines	Hemolytic anemia with methemoglobinanemia	2 (2)
19	Hydroquinones	Hepatotoxicity	2 (2)
20	Imidazole-2-thione derivatives	Thyrotoxicity	2 (4)
21	N-Alkyl-N'-phenyl-p-phenylenediamine	Hemolytic anemia with methemoglobinanemia	2 (2)
22	Nitrobenzenes	Hemolytic anemia with methemoglobinanemia	12 (13)
23	Nitrobenzenes	Hepato toxicity	12 (13)
24	Nitrobenzenes	Testicular toxicity	4 (5)
25	Nitrophenols/Halophenols	Energy metabolism dysfunction	12 (12)
26	o-/p-Aminophenols	Hemolytic anemia with methemoglobinanemia	3 (3)
27	Organophosphates	Neurotoxicity	8 (9)
28	Oximes	Hemolytic anemia with methemoglobinanemia	3 (3)
29	p-Alkylphenols	Hepatotoxicity	7 (7)
30	p-Aminophenols	Renal toxicity	2 (2)
31	Phenols	Mucous membrane irritation	25 (25)
32	Phenyl phoshates	Lipodosis of adrenocortial	4 (5)
33	Phthalate esters	Testicular toxicity	3 (3)
34	Hydroquinones	Hepatotoxicity	2 (2)

Table 2. Result of the Validation of HESS Profiler

Validataion Set	# of Chemicals in the Validataion Set	# of Chemicals Classified by HESS Profiler	% of Chemicals classified by HESS profiler	# of Chemicals Correctly Classified by HESS Profiler	% of Chemicals Correctly Classified by HESS Profiler
CSCL	99	35	35	26	74
COSMOS	118	20	17	14	70
ToxREf	428	49	11	40	82
Total	638	104	16	80	77

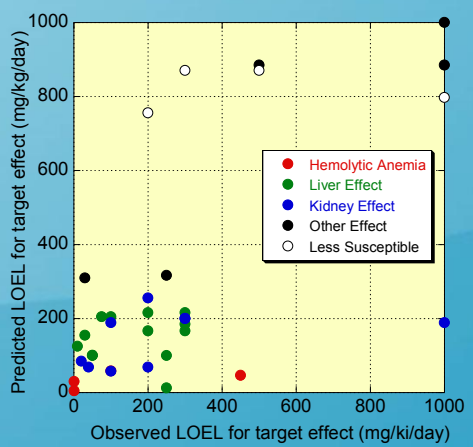

Fig.2 Predictivety of read-across for CSCL data