Original Article

Thesaurus for histopathological findings in publically available reports of repeated-dose oral toxicity studies in rats for 156 chemicals

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ABSTRACT — Because histopathological findings are often conclusive indicators of the toxicities of chemicals, standardization of nomenclature and construction of a thesaurus for histopathological findings are important for the comparative evaluation of histopathological data from repeated-dose toxicity studies (RTS). However, terms for histopathological findings have not been standardized and different technical terms are used to indicate almost the same thing in RTS. The present study was conducted to construct an easy-to-use thesaurus for histopathological findings in order to facilitate hazard assessments of untested chemicals by the category approach using knowledge of the toxicity of analogue chemicals. We used reports of 28-day RTS, conducted on rats by gavage, which were posted on the websites of the National Institute of Health Sciences (NIHS) and the National Institute of Technology and Evaluation (NITE). The histopathological data were from 156 reports on RTS conducted by 13 institutions in Japan. As a result of this study, major parts of the thesaurus were devoted to the findings in the liver, kidney, stomach, adrenal, thyroid and testis; the first three organs are known to be the main targets of chemicals. We also decided that findings such as swelling and enlargement of hepatocytes should be categorized as synonyms for terms meaning hypertrophy. Our thesaurus will be helpful in assessing or screening new untested chemicals by the category approach using knowledge of the toxicities of analogues of the new chemical. The RTS database with this thesaurus will be made publically available in 2012.

Key words: Pathology thesaurus, Histopathological findings, Repeated-dose oral toxicity studies, Rat, Chemical compounds

INTRODUCTION

Standardization of nomenclature and the construction of a thesaurus for histopathological findings are important for the proper comparative evaluation of the histopathological data from different repeated-dose toxicity studies (RTS). There are a number of endpoints for hazard identification in RTS such as body weight change, organ

weights, and hematological and blood biochemical examinations. Among them, histopathological findings can be unique indicators because a number of findings are qualitatively diagnosed by toxicologic pathologists, and these qualitative assessments are often conclusive or sensitive indicators of toxicities induced by chemicals. However, the descriptive terminology for histopathological findings, especially non-neoplastic lesions, has not yet been stand-

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ardized and various histopathological terms with identical meanings are used in different laboratories or among pathologists who conduct RTS, whereas neoplastic terminology has been already globally harmonized (International Agency for Research on Cancer, IARC). Thus, to facilitate hazard identification of chemicals it is necessary to classify the chaotic histopathological findings and link related terms in a thesaurus.

With the global need for quantitative hazard assessment, and because of public opinion opposing the use of animals in chemical testing, the OECD (as well as other prominent organizations) is developing the basis for (quantitative) structure-activity relationships {(Q)SAR}, also known as the category approach for RTS. Papers describing databases for repeated-dose toxicity studies of commercial chemicals are now appearing e.g. Bitsch *et al.* (2006).

Recently, we have had an opportunity to analyze 28-day RTS data for existing chemicals under the Japanese Chemical Substances Control Law in order to establish a category approach for the RTS database (Nishikawa *et al.*, 2008; Sakuratani *et al.*, 2008) as a part of the New Energy and Industrial Technology Development Organization (NEDO) grant funded project called Development of Hazard Assessment Techniques Using Structure-Activity Relationship Methods. To facilitate efficient searching for important information in the RTS database, it is necessary to develop a pathology thesaurus containing tech-

nical terms that appear in these reports.

In this paper, we describe the construction of a pathology thesaurus for the category approach, which systematically associates synonyms of the technical terms used in RTS reports. In the present study, this process has been checked and supervised throughout the study by several toxicologic pathologists.

MATERIALS AND METHODS

We used reports of 28-day RTS conducted on rats, which were posted on the websites of the National Institute of Health Sciences (NIHS) and the National Institute of Technology and Evaluation (NITE). These studies were conducted in accordance with Guidelines for 28-Day Repeat Dose Toxicity Test of Chemicals (Japan).

Histopathological data from 156 reports from 13 institutions in Japan were used. These institutions are listed in Table 1.

The classification of the histopathological findings was conducted by pathology (Toshio Imai, Satoshi Nishikawa and Midori Yoshida) and IT (Tatsuhiro Yamashita) experts. All histopathological findings observed in the 156 reports were first listed and then given a preferred term by experienced pathologists certificated by the Japanese Society of Toxicologic Pathology (JSTP). Then, more detailed and supplementary concept descriptions of the findings including cell typing or dis-

Table 1. List of institutions

1	Biosafety Research Center, Foods, Drugs and Pesticides
2	Bozo Research Center Inc.
3	Food and Drug Safety Center
4	Ina Research Inc.
5	Mitsubishi Chemical Safety Institute Ltd.
6	National Institute of Health Sciences
7	Nihon Bioresearch Inc.
8	Nippon Experimental Medical Research Institute Co., Ltd.
9	Nissei Bilis Co., Ltd.
10	Panapharm Laboratories Co., Ltd.
11	Research Institute for Animal Science in Biochemistry & Toxicology
12	Safety Research Institute for Chemical Compounds Co., Ltd.
13	Shin Nippon Biochemical Laboratories, Ltd.

tribution/sites were added by the pathology experts. To make searching the reports for histopathological findings easier, we adopted a tree structure to show the thesaurus. The findings listed were arranged in the order of system, organs, histopathological findings, cell typing and distribution/sites to facilitate smooth search operations by IT experts. For instance, single cell necrosis in the centrilobular area in the liver is listed and expressed as liver, necrosis, single cell, or centrilobular. Incomprehensive or unclassified terms are classified in miscellaneous (misc). All the processes described above were checked and reviewed several times by experienced toxicologic pathologists.

RESULTS AND DISCUSSION

Terms obtained from the 156 reports are shown in Fig. 1. Eleven systems, 59 organs and a total of 411 histopathological findings derived from 4,263 original histopathological terms, as well as other detailed information, have been arranged. The terms used varied depending on the laboratories, but the three organs showing the most histopathological findings were the liver, kidney, and stomach and this is reflected in the thesaurus.

In the liver, findings such as centrilobular hypertrophy of hepatocytes were widely found, and terms meaning swelling and enlargement were categorized as synonyms. In the kidney, changes in the tubular epithelium were widely observed. In particular, many reports of hyaline droplet deposition and basophilic changes of the proximal tubule were found in males; however, only one case reported changes of the glomeruli. In the stomach, where chemicals were orally administered, findings related to the gavage treatment such as squamous hyperplasia, keratosis, ulcer, erosion, edema and cell infiltration of the forestomach were frequently found.

Moreover, in the endocrine system, vacuolation/lipid droplet formation in the cortical cells of the adrenal gland and follicular cell hypertrophy of the thyroid gland were widely seen, the latter findings being possibly related to changes due centrilobular hypertrophy of the hepatocytes. In the reproductive system, findings such as degeneration/atrophy of seminiferous tubules in the testis were found. Findings such as hypoplasia and disappearance of spermatogonia were considered to be synonyms. On the other hand, common terms also existed for findings in many organs. Various types of cell infiltration were the commonest term in this present thesaurus.

Through developing a thesaurus, it has become clear that many common findings on various organs have been reported in 28-day RTS. In identifying the three most

affected organs, the nomination of the liver and kidney was a reflection of the fact that these organs represented the main target organs of many chemicals. The nomination of the stomach might be related to the direct exposure of the stomach mucosa to the test substances, because gavage by gastric tube is a designated administration route in RTS. The study also showed that there are also organ specific findings induced by chemicals which were toxicologically important such as toxicity to the nervous system. Where their incidences were not frequent, they were considered for exclusion in the construction of the thesaurus.

Because pathological terms are complex and interpretation requires high levels of expertise, it is difficult to standardize the terms for histopathological findings; however, the International Harmonization of Nomenclature and Diagnostic Criteria for Lesions in the Rat and Mouse (INHAND) and the Global Editorial and Steering Committee (GESC) are now developing a pathology thesaurus to be used globally. In the context of such international development, and since it is important to know what kind of findings are observed in actual toxicity testing, the thesaurus we are developing will be helpful to pathologists in describing pathological findings.

As part of the NEDO project, we have had an opportunity to analyze 28-day RTS data for existing chemicals under the Japanese Chemical Substances Control Law in order to establish a category approach for the RTS database (Nishikawa *et al.*, 2008; Sakuratani *et al.*, 2008). Since it is important to compare histopathological findings of RTS of chemicals with similar structural features in using the category approach, it is necessary to develop a pathology thesaurus containing technical terms that commonly appear in RTS reports. For example, we decided findings such as swelling and enlargement of hepatocytes should be categorized as a synonym for terms meaning hypertrophy.

The present study was conducted to construct an easy-to-use thesaurus for histopathological findings and which covers detailed information including target cell typing and distribution/sites found in disclosed reports on 28-day RTS in rats. Each pathological finding and more detailed descriptions are available using the tree structure developed in the present study. This thesaurus will be useful for the hazard assessment of untested chemicals by the category approach using analogue chemicals. The RTS database with this thesaurus will be made publically available in 2012.

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