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What is This?
The Value of Historical Control Data—Scientific Advantages for Pathologists, Industry and Agencies

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ABSTRACT

Historical control tumor data are useful in the interpretation of long-term rodent carcinogenicity bioassays, especially to assess the occurrence of rare tumors and marginally increased tumor incidences. The major prerequisites to compare historical control data with studies under evaluation are the validity and consistency of the respective databases. The RITA (Registry of Industrial Toxicology Animal-data) database for historical data of tumors and pre-neoplastic lesions collects data according to highly standardized procedures including tissue sampling and trimming, histopathology according to internationally harmonized nomenclature and diagnostic criteria, and peer review. All lesions that are entered are unanimously diagnosed according to IARC (International Agency for Research on Cancer)/WHO criteria. The validity of data is additionally confirmed by a complete peer review performed by a database pathologist. Equivocal diagnoses and selected cases are additionally submitted to a panel of RITA pathologists. In the RITA database, there are currently 10,896 rats from 106 studies with more than 17,604 primary tumors and 16,551 pre-neoplastic lesions. The RITA database for historical control data for Wistar and Sprague Dawley rats as well as for different mouse strains is briefly described. Based upon RITA background data, the survival rate of Wistar rats has been consistent over a period of 10 years. The occurrence of tumor-bearing animals also shows a stable percentage over a decade. Additionally, examples of how historical control data may support carcinogenic risk assessment in cases of rare tumors or marginally increased incidences of tumors and pre-neoplastic lesions are given.

Keywords: Rodents; rat; mouse; neoplastic lesions; pre-neoplastic lesions; histopathology; pathology; historical control data; survival rate; RITA.

INTRODUCTION

Long-term carcinogenicity studies are conducted to evaluate the carcinogenic risk of xenobiotics by comparing the incidences of neoplastic and pre-neoplastic lesions in laboratory animals observed in the dose groups with those in the concurrent control. Due to the high degree of comparability with dosed animals, the concurrent control group is considered to be the most critical control (1, 2). Nevertheless, in case of atypical frequencies of neoplastic or pre-neoplastic lesions, there are certain limitations of the concurrent control. A lower than normal tumor frequency in the concurrent control animals may lead to a statistically significant increased incidence of lesions in the dose groups. A higher than normal tumor frequency in the concurrent control, on the other hand, might mask a carcinogenic response in dosed animals. In such cases historical control data may support substantially the assessment of a potential carcinogenic risk. The major difficulty in using historical control data is the comparability with the study under evaluation concerning major sources of variability such as animal room environment, dietary factors, body weight, age, sex, gross necropsy, slide preparation procedures, and histopathology diagnoses (2, 3). Therefore, standardized procedures and extensive background information on any study entered into a database is needed.

RITA DATABASE

RITA (Registry of Industrial Toxicology Animal-data) is a pathology database founded in 1988 in Hannover by a cooperation between the Fraunhofer Institute of Toxicology and Aerosol Research, Hannover (FH-ITA) and 13 pharmaceutical and chemical companies from Germany and Switzerland. RITA was created with the objective of establishing a centralized European database providing standardized and valid historical background data for carcinogenic risk assessment. Currently, companies from all over Europe1 are participating in the RITA Group, providing data from carcinogenicity studies to be stored in the database. In this computerized database, neoplastic and pre-neoplastic lesions observed in control animals are collected according to standardized rules. From the start of the RITA project there was general agreement among the participating companies that standardization was considered to be one of the major basic requirements of a valid database as various factors influence the quality of the tumor data collection (1, 4, 5). For the purpose of

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1 Astra-Zeneca, Aventis Pharma, BASF AG, Bayer Ag, Boehringer Ingelheim Pharma, Byk-Gulden Pharmaceuticals, Hoffmann-La Roche, Knoll AG, Merck KgaA, Syngenta AG, Novartis Pharma, Pfizer Amboise, Pharmacia.

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comparability, various study-related information including study duration, study design, housing, environmental conditions such as temperature, humidity, light cycles, characterization of bedding material and diet, and parameters on food intake and dietary constituents are acquired so that more than 50 individual data items per study are stored. In addition, animal-related data such as information on the commercial breeder, strain, sex of the individual animal, age, animal status and many other parameters are entered (2, 6, 7). Sampling and trimming of organs and tissues have also been standardized among the RITA companies and documented in Standard Operating Procedures (8). Diagnostic criteria and nomenclature of pre-neoplastic lesions and tumors provide a major source of variability of historical control data. For that reason, the RITA group developed standardized diagnostic criteria and nomenclature in close cooperation with representatives from the United States and Japan. The standardized nomenclature and diagnostic criteria have been published by IARC: International Classification of Rodent Tumors Part 1: The Rat and by Springer Press: International Classification of Rodent Tumors: The Mouse. All diagnoses are accordingly stored in the RITA database.

**DATA TRANSFER AND VALIDATION**

Following quality assurance procedures similar to those used by the National Toxicology Program (NTP) (5, 9, 10), the incidences of neoplasms and pre-neoplastic lesions are checked for consistency and completeness at the testing laboratory before they are entered into the data acquisition software, Registry Input Program (REGINA) for RITA (Figure 1). The carcinogenicity studies are, in many cases, peer reviewed by a second pathologist in the testing facility before submission. The delivered study data, group data, animal data, and findings are verified in the REGINA system for consistency and completeness and entered in a preliminary database, where a complete data check is performed. This is followed by a peer review of all pre-neoplastic and neoplastic lesions observed in the control animals combined with an additional check of all tissues from 10% of animals randomly selected. The peer review is performed by a pathologist of the FH-ITA and includes checking on diagnostic criteria and nomenclature. Diagnostic differences of opinion are discussed by a panel of pathologists from the participating companies and FH-ITA to decide on a final diagnosis. In order to increase the consistency and validity of entered data (5), various special stains and tumor/cell markers are regularly applied to detect cytoskeletal and extracellular matrix proteins (e.g., pan-cytokeratin, vimentin, S100, desmin, actin, von-Willebrand-factor), hormones and enzymes (e.g., prolactin, ACTH, calcitonin, insulin, chromogranin, synaptophysin, tyrosine hydroxylase, PgR, GSTPi), lymphoid cells and macrophages (e.g., CD3, CD8, CD45, CD79α, ED1, F4/80, Mac-2, Mac-3) and cell-proliferation markers (e.g., PCNA, Ki-67) to better categorize neoplastic lesions in equivocal cases. Following this intense peer review procedure, lesions are transferred into the RITA database after a final check of data (Figure 1). The data collected in the RITA/RENI (Registry Nomenclature Information System) system are the basis for the generation of reports on historical control data. As of May 2001, 106 rat studies and 37 mouse studies had been...
TABLE 1.—Status of RITA database (May 2001).

<table>
<thead>
<tr>
<th></th>
<th>Rat</th>
<th>Mouse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of studies</td>
<td>106</td>
<td>37</td>
</tr>
<tr>
<td>Number of animals</td>
<td>10,896</td>
<td>3,572</td>
</tr>
<tr>
<td>Primary tumors</td>
<td>17,604</td>
<td>3,056</td>
</tr>
<tr>
<td>Pre-neoplastic lesions</td>
<td>16.551</td>
<td>1,833</td>
</tr>
</tbody>
</table>

entered into the database comprising more than 10,000 rats and 17,604 primary tumors (Table 1).

APPLICATION OF DATA GENERATED IN THE RITA DATABASE

In addition to comparing tumor incidences in rodent bioassays with historical control data entered in the RITA database, the database can also be used to check for parameters such as survival rate of animals, tumor-bearing animals, consistency of tumor incidences over different time windows, and tumor incidences for different commercial breeders. The knowledge of this information and various other parameters stored in the database as background data supports the proper use of historical control data during the evaluation of carcinogenicity studies for risk assessment.

SURVIVAL RATE OF LABORATORY RODENTS

The 2-year survival rates in F344 rats show a time-dependent decrease corresponding to an increase in body weight in NTP long-term carcinogenicity studies (5). A similar decrease in survival rate of control Sprague-Dawley rats has also been described (5, 11). The major causes of death in male F344 rats were leukemia, pituitary gland neoplasm and severe nephropathy (5, 12). A similar decrease in 2-year survival rate has not been observed in Wistar rats used in the RITA database. The survival rate of Wistar rat strains has been analyzed over a time frame of 10–12 years. During this observation period lasting from 1983 to 1993/95 the 2-year the mean survival rate was 81% and ranged from 76% to 89%. Thus, there has not been a fundamental decrease but a quite constant survival rate in the Wistar rats used by RITA companies over a decade observation period (Figure 2).

TUMOR-BEARING ANIMALS

A constant pattern of RITA data is also seen concerning the percentage of tumor-bearing Wistar rats over an observation period of 10 years lasting from 1983 to 1993 (Figure 2). Animals with primary tumors ranged between 58% and 92%. Rats bearing one tumor ranged between 31% and 44%. Wistar rats with two neoplasias ranged from 12% to 39%. The percentage of Wistar rats developing three (5% to 16%) and four (0% to 7%) tumors was also quite constant. For the specific commercial breeders as well (breeders A, B and D), the incidences of primary tumors remained relatively constant over the 10-year observation period (Figures 3–5).

CONSISTENCY OF TIME-RELATED TUMOR INCIDENCES

Time (calendar year) is considered to be an important source of variability in tumor rates. Different types of tumors exhibited increased incidences in studies relative to earlier experiments (1, 5). Due to this time-related variability of tumor incidences, historical control data should be
limited to more recent studies. For that reason, windows of 3–4 years or even 5 years are proposed (1, 2). In order to analyze time-related shifts in tumor incidences, the occurrence of Leydig cell adenomas and mammary gland fibroadenomas in Wistar rats, as examples, were investigated over an observation period of 12 years. The data show a quite constant mean percentage of 39% for Leydig cell adenoma for breeder A, whereas for breeder G there was a slight increase in the...
percentage of tumor incidence within the 12-year time frame (Figure 7). According to these data, a window of more than 3–5 year might be applicable to specific tumors in strains which exhibit a constant incidence of tumor occurrence over time. On the other hand, narrow time windows should be used for tumors like mammary gland fibroadenomas (Figure 8), which increased in Wistar rats from approximately 10% to >25% for commercial breeder G and decreased from approximately 20% to < 10% during the same observation period for breeder A.

**HISTORICAL TUMOR CONTROL DATA SUPPORTING CARCINOGENIC RISK EVALUATION**

The most appropriate control group in long-term bioassays is the concurrent control, which is compared with the experimental groups. However, when there is increased occurrence...
In a case of significantly increased incidences of pituitary adenoma of the pars distalis in female Wistar rats, historical control data of the RITA database have been applied. The tumor incidences ranged from 14 (28%) in the concurrent controls.
control to 24 (48%) in the high dose group (Table 2). There were 55 studies conducted with Wistar rats comprising 3,098 animals with 1,707 adenomas of the pars distalis, which were entered into the RITA database. The mean percentage of all adenomas was 55.1% and the range was from 15% to 80%. For the specific commercial breeder of this Wistar strain, there were 16 studies found in the RITA database with 797 animals bearing 342 tumors. The mean percentage of the tumor incidence was 42.9%, the range was 31.2% to 62%. At the level of the company for this specific strain, there were 11 studies entered in the database with 558 animals and 248 adenomas of the pituitary gland (Table 2a). The mean percentage was 44% and the range 32% to 62%. With pituitary adenomas of the pars distalis in female Wistar rats, study incidences over an observation period of 14 years could be used for this specific strain due to the constant time-related development of tumor incidences (Figure 9). With this information from the RITA database, the increase of pituitary adenomas of the pars distalis in rats seen in the long-term bioassay was considered to be within the range of historical control data. In addition, there was no increase in adenomas of the pars distalis in the pituitary gland in males and there was also no increase in hyperplasias of the pars distalis in either sex. Therefore, the positive trend seen in this study was due to a distinctively low concurrent control incidence.

In the case of focal hyperplasias of Leydig cells in male Wistar rats, there was also a significant trend seen in a carcinogenicity study. The incidence ranged from 4 (8.0%) in the controls up to 9 (18%) hyperplasias in the high dose males (Table 3). This incidence was covered by the mean percentage of 23.8% seen in all studies with Wistar rats in the RITA database. The percentage of 18% in the respective study was also close to the mean values for Wistar rats from the specific commercial breeder and was also covered by the incidences of the company-specific studies entered into the RITA database (Table 3a).

Besides the evaluation of marginally increased tumor incidences or incidences of pre-neoplastic lesions, historical control data may be also applied to judge increased incidences of rare tumors. In the case of transitional cell papillomas of the urinary bladder in female Wistar rats, there was an increase seen in a long-term rodent bioassay. In high dose females only, five (10%) transitional cell papillomas were observed (Table 4). In 55 studies in the RITA database with Wistar rats, seven (0.2%) transitional cell papillomas were observed. For the specific commercial breeder, there were three papillomas seen in 776 rats, although there were no transitional cell papillomas in 240 animals from company-specific studies (Table 4a). Thus, the historical control data of the RITA database clearly

Table 2.—Tumor incidence of pituitary gland adenoma of the pars distalis in female Wistar rats.

<table>
<thead>
<tr>
<th>Group</th>
<th>Control</th>
<th>Low dose</th>
<th>Mid dose</th>
<th>High dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of animals</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Number of tumors</td>
<td>14</td>
<td>22</td>
<td>20</td>
<td>24</td>
</tr>
<tr>
<td>Incidence (%)</td>
<td>28.0</td>
<td>44.0</td>
<td>40.0</td>
<td>48.0</td>
</tr>
</tbody>
</table>

Table 2a.—RITA historical control data of pituitary gland adenoma of the pars distalis.

<table>
<thead>
<tr>
<th>Source</th>
<th>Number of studies</th>
<th>Number of animals</th>
<th>Number of tumors</th>
<th>Mean (%)</th>
<th>Range (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RITA, all Wistar</td>
<td>55</td>
<td>3,096</td>
<td>1,707</td>
<td>55.1</td>
<td>15.0–80.0</td>
</tr>
<tr>
<td>Breeder, Wistar</td>
<td>16</td>
<td>797</td>
<td>342</td>
<td>42.9</td>
<td>31.2–62.0</td>
</tr>
<tr>
<td>Company, Wistar</td>
<td>11</td>
<td>558</td>
<td>248</td>
<td>44.4</td>
<td>32.7–62.0</td>
</tr>
</tbody>
</table>

![Figure 9](https://via.placeholder.com/150)

**Figure 9.**—Incidence of pituitary gland, adenoma, pars distalis, female Wistar rats for different breeders.
showed that there are very low tumor incidences in control animals which do not overlap the incidences observed in the carcinogenicity study. Therefore, the company considered this tumor response to be treatment-related.

Historical tumor control data from a standardized database like RITA may provide substantial information to evaluate the carcinogenic risk of compounds for pathologists, agencies and industry. These data support the interpretation of rare occurring tumors, marginally increased pre-neoplastic lesions and tumors, and atypically high or low concurrent control tumor incidences. Additionally, the RITA database provides additional information on background data such as survival rates, tumor-bearing animals, specific commercial breeder incidences, etc. which allow proper use of historical control data in assessing studies under evaluation.

REFERENCES