Chapter 6
History and Current Regulatory Requirements

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Abstract The assessment of risk to humans of cancer following exposure to chemicals has been a challenging process for decades. The early pragmatic approaches to this important challenge have evolved with growing understanding of the underlying biology of the cellular processes that lead to tumor development in animals and the relevance of these findings to human risk. The regulatory approaches to assessment of human risk of cancer in place today reflect the current state of understanding of these complex biological processes while providing a common regulatory framework for risk assessment. This chapter reviews the evolution of this process from the early days to the current state setting the framework for further evolution of how we address this critical challenge.

Keywords Bioassay history • FDA CAC • Rodent bioassay • Human risk assessment • ICH carcinogenicity guidelines • HESI Alternatives to Carcinogenicity Testing

There can be no question that exposure to some chemicals can result in the formation of tumors in humans. Since the early observations by Percival Pott of scrotal and nasal cancer in chimney sweeps in England in the 1700s [27] it has become well accepted that chemical exposure can, under certain conditions, result in human cancer. The challenge posed by this observation (and many others in subsequent years) has been and continues to be how to predict prospectively which chemicals pose carcinogenic hazards to humans under the conditions of use. This challenge takes on various dimensions as one considers occupational or environmental exposures versus those posed by deliberate application of chemicals in the context of therapeutic approach to human diseases. In the latter case, generally much more information is available on the nature of the chemical and how it interacts with biological

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systems including extensive safety testing in the exposed human population. In addition, the exposure has a presumed positive outcome so there is the opportunity to consider a risk-benefit analysis when evaluating the body of data. This chapter will limit the discussion of this broad topic to the subset of pharmaceutical chemicals and the particular challenges posed by these chemicals.

6.1 Early History

Research in the mid-1960s with classes of chemicals known to be carcinogenic to humans demonstrated that a similar tumorigenic response could be reproduced in animals after topical or oral administration [24, 27]. These chemicals were from classes of chemicals that are now well known to represent highly reactive and largely genotoxic chemicals such as polycyclic aromatic hydrocarbons, azo and acridine dyes, and aromatic amines and nitrosamines ([43], 40]). This observation that human tumors could be produced in animals with the same chemicals of concern led to the general concept that exposure of test animals to chemicals could predict human cancer. As greater general concern over the potential for chemicals to cause cancer grew along with the awareness of the vast number of new chemicals for which little information was available, the US National Cancer Institute proposed formal procedures for evaluating the carcinogenic potential of chemicals in the early 1960s ([3], 54]). In these proposals, it was envisioned that animal tests would identify chemicals of concern which warranted further study rather than the idea that a single study or set of studies would provide the definitive determinant of the human carcinogenic potential of a chemical [3]. Despite this reasoned approach to the challenge, the desire for a quick and simple way to identify (and remove) human cancer hazards led to the development of the recommendation in 1975 that subsequently became the basis for regulatory guidance for both environmental/industrial and pharmaceutical chemicals [48]. This guidance led to the currently accepted practice of the use of 2 year studies in two rodent species in what is generally referred to as the rodent bioassay [3]. This remains the standard today for assessment of human risk of cancer from chemical exposure.

The Sontag guidelines were published by the US National Cancer Institute in 1976 [48] and quickly became the de facto standard for assessing the carcinogenic potential of chemicals in animal studies. These guidelines gave detailed descriptions of how a rodent bioassay should be conducted and found their way into federal guidelines in the ensuing years [45]. These documents clearly described the approaches to design of the 2 year rodent studies in rats and mice including the practice of using the maximum tolerated dose (MTD) to select the top dose in these studies. The principles articulated by the NCI guided how data from these studies were used. Important among these principles was the concept that chemicals that produced tumors in rodents were assumed to present human risk and that tumors produced at a high (toxic) dose were assumed to be predictive of a tumorigenic response at lower doses [6, 45].

In the almost four decades since the guidelines for the rodent bioassay were first formally published, much has been learned about the utility of using data from these assays for human risk assessment. It has become clear that what was envisioned as a simple and efficient process for identifying potential human carcinogens is much more complex than originally thought. This complexity arose from several sources. These will be explored below in an attempt to illustrate how the continuing exploration of confounding data has led to (and is still leading to) our current understanding of how best to approach the important and difficult challenge of predicting human risk of cancer.

6.2 Growing Experience: Factors Impacting the Interpretation of Rodent Bioassay Data

When the overall body of data from rodent bioassays is considered, it can be shown that there are many more positive studies in rodents than would be expected from the relatively few known human carcinogens [41, 53]. The basis for this high rate of positive outcomes can be attributed to one or more of several factors: (1) the use of a high (toxic) dose as the top dose in the study, (2) secondary mechanisms of carcinogenicity unique to the rodent, and (3) other species-specific responses.

The available data show a high degree of concordance between the magnitude of the dose used in the bioassay and the production of tumors in rodents [20, 37]. The rationale for using the highest testable dose is that this maximizes the sensitivity of the bioassay and attempts to compensate for the limited number of animals that can be exposed in the testing environment. The consequence of this approach, however, is that mechanisms that may operate only at toxic doses may trigger processes that result in rodent tumors at the end of a 2 year study [1]. This concern over the impact of such an artificial experimental construct led to the adoption of alternative means of dose selection for these 2 year studies for pharmaceutical chemicals that will be discussed in more detail below.

As more information became available particularly with pharmaceutical compounds tested in 2 year bioassays in the 1980s and 1990s, more evidence accumulated for tumorigenic responses in rodents that were not representative of what would occur under similar exposure conditions in humans. An early observation that paved the way for a desire for more detailed mechanistic studies in evaluating rodent tumor data was the observations with soterenol. The development of this drug was stopped in the early 1970s due to the development of mesovarial leiomyomas in a 2 year study in rats. Over a period of years, it was demonstrated that this response in rats was entirely mediated by excessive β_2-adrenergic receptor stimulation and that the comparable tissue in humans does not contain this essential target [31, 32] demonstrating the species specificity of this tumorigenic response.

The so-called “secondary mechanisms” of carcinogenesis have become a more widely accepted explanation for the observation of tumors in rodents for non-genotoxic compounds. Examples of these responses include mammary tumors

secondary to drug-induced alterations in prolactin levels, testicular Leydig cell tumors secondary to drug-induced increases in luteinizing hormone (LH) levels, and thyroid follicular cell tumors secondary to drug-induced increases in thyroid stimulating hormone (TSH) levels [32, 38]. Similar strong evidence was developed over many years to demonstrate why drug-induced increases in serum gastrin levels resulted in ECL cell carcinoid tumors in the stomach of rats treated with proton pump inhibitors (e.g.: omeprazole) and did not predict human tumors [4, 21, 28].

In addition to these endocrine tumors, more evidence accumulated over the years of use of the bioassay to show why some positive results in the bioassay did not predict human cancer [33]. While not specifically relating to pharmaceuticals, the demonstration that the chronic irritation and proliferative response induced in the rat bladder by sodium saccharin induced a proliferative response unique to the rodent that led to tumors in this species [5] was an important contribution to the understanding of the importance of evaluating the global weight of evidence when evaluating the significance of rodent tumors in 2 year bioassays. Similarly, the demonstration of the relationship between the appearance of so-called "hydrocarbon nephropathy" in male rats and the subsequent chronic irritation, cell proliferation and tumorigenesis with agents that bound to α2 microglobulin led to the understanding today that, for agents that can be demonstrated to act by this mechanism, rodent tumors are not considered predictive of human risk [13, 30]. Yet another example of such "secondary mechanisms" are rodent liver tumors resulting from the sustained proliferative stimulus induced by CYP enzyme inducers such as phenobarbital [19, 35, 39]. An understanding of the molecular mechanisms associated with this sustained proliferation in the rodent and the marked differences in this biology from what is observed in humans under the conditions of exposure has led to the general understanding that hepatocellular tumors that arise in rodents after prolonged exposure to such agents do not predict human risk.

6.3 A Focused Search for Better Alternatives

Over the several decades of accumulated experience with the rodent bioassay, much has been learned about how chemicals cause cancer. Our understanding of this process is very different from when the rodent bioassay was conceived and instituted. We have learned much about how pharmaceuticals (as well other chemicals) produce rodent tumors and how to interpret these findings in terms of human risk [17, 18]. The continuing problem, however, has been (and remains) the fact that the rodent bioassays take approximately 3 years to complete from initiation of dosing to final statistical evaluation of tumor data and cost from three to five million US dollars at today's prices. In addition, much time can be required to perform any mechanistic studies that may be required to put any tumor findings in perspective and understand the significance for human risk. There has been, therefore, an increasingly urgent search over the past 10–15 years for alternative approaches to the challenging task of prediction of human cancer risk particularly for non-genotoxic chemicals.

These concerns, the increasing understanding of mechanisms of non-genotoxic carcinogenicity, and the growing uncertainties around how best to interpret data derived from the 2 year bioassays led to the formation of a Expert Working Group within the ICH framework in the early 1990s and drove the discussions in this group. . The EWG initiated a retrospective examination of the pharmaceutical databases in the three regulatory regions involved in ICH (FDA – US, CPMP – Europe, MHW – Japan) and provided data that showed approximately one half of the tested compounds were positive in one or both of the two species used in the 2 year bioassays [10, 42, 53]. This exercise led one group (CHMP Safety Working Party) to conclude that little additional information of importance in human risk assessment was gained from the mouse data and put the position forward that only one species was necessary to support drug registration [53]; this opinion was not shared by the members of the other two regulatory regions.

Concurrent with the ICH discussions was the growing awareness from reports in the literature that genetically modified rodents could detect signals associated with the carcinogenic response ([50]; p53 knockout mouse: [15]; Tg.rasH2 transgenic mouse: [2]; Tg.AC mouse: [29]; XPA repair deficient mouse: DeVries [14]). Of the models that had been proposed at the time leading up to ICH III in the late 1990s, four in vivo assays were brought forward for discussion within the ICH Expert Working Group: Tg.AC knockout mouse, p53 hemizygous knockout mouse, rasH2 transgenic mouse, and the XPA repair deficient mouse. Additional models considered by the group were the newborn mouse and the in vitro SHE cell transformation assay. In a landmark publication in 1997, the US FDA stated that there was sufficient information available with several of the in vivo models to employ one of these alternative assays instead of a second species in assessing the carcinogenic potential of pharmaceutical chemicals [10]. All three regulatory authorities involved in the ICH process agreed to this in the ICH S1b guideline: "Testing for the Carcinogenic Activity of Pharmaceuticals" in that same year.

As the in vivo models had not been fully characterized with pharmaceutical chemicals at the time of the signing of this ICH guideline, a group of academic, government, and industry scientists launched a large collaborative program through the International Life Sciences Institute Health and Environmental Sciences Institute (ILSI/HESI) organization to more fully understand how best to utilize these alternative models [46]. Twenty one chemicals were evaluated including known human carcinogens, known human non-carcinogens, genotoxic and non-genotoxic chemicals in five alternative models (p53 hemizygous knockout mouse, Tg.AC transgenic mouse (using both topical and oral administration), rasH2 transgenic mouse, XPA knockout and XPA/p53 knockout mouse). In addition to these genetically modified in vivo models, the chemicals were tested in the neonatal mouse and the in vitro SHE cell transformation assay [7]. With the exception of the SHE assay and the neonatal mouse where the data were not considered sufficiently informative, the results of the studies with the other models enabled them to be used with confidence in the assessment of novel pharmaceutical compounds [16, 49, 52].

Based on the outcome of the HESI program, there was general acceptance of the use of these alternative genetically modified mouse models in both industry and

regulatory agencies as screening tools. While it was initially hoped that the results of studies with these genetically modified mouse models would offer important insight into mechanism, it is clear that the genetic manipulations merely serve to enhance the sensitivity of the animal to a carcinogenic stimulus without giving information useful for mode-of-action analysis or specific tissue sensitivity [8] FDA (and agencies in other regulatory regions) generally accepts the p53 knockout mouse for evaluation of the carcinogenic potential of genotoxic agents, the rasH2 transgenic mouse for genotoxic or non-genotoxic compounds, and the Tg.AC transgenic mouse only for dermal products applied topically [25]. As of 2003, 81 protocols had been submitted for approval to the FDA using genetically modified mice [25] and as of 2005, 40 reports of completed studies with these models had been submitted to FDA [23]. Most of the protocols submitted to the FDA for approval after 2004 have employed the rasH2 mouse model [23].

6.4 Current Regulatory Approach to the Design of Studies for Carcinogenic Risk Assessment for Pharmaceuticals

6.4.1 FDA's Carcinogen Assessment Committee (CAC) and Executive CAC (eCAC)

The CAC and eCAC were established in the Center for Drug Evaluation and Research's (CDER) Office of New Drugs (OND) in the late 1980s. The need for this activity was recognized by Dr. Robert Temple (currently the Deputy Director for Clinical Science) to assure a uniform approach to study design and data interpretation across CDER and it was his leadership that led to their creation. The need for such a body becomes clear when one considers that many drugs are approved for a variety of indications. For example, duloxetine is approved for the treatment of depression, anxiety, fibromyalgia and back pain. Different indications can be regulated by different review divisions within OND. Individual divisions reviewing the same carcinogenicity studies but coming to differing conclusions could lead to regulatory chaos. As a result, OND established the eCAC and the CAC to be the final arbiter for interpreting the outcomes of carcinogenicity studies.

Other national drug regulatory bodies do not have the equivalent of CDER's eCAC. However, the Japanese and European Union regulatory bodies are signatories to ICH guidelines S1, S1A, S1B and S1C. If carcinogenicity studies are performed in conformance with these guidelines, the final results should be acceptable in all regions.

The eCAC is chaired by the pharm/tox associate director, and includes Pharmacology/Toxicology Office of Drug Evaluation (ODE) associate directors, one rotating pharm/tox supervisor and an executive secretary. The committee meets on a weekly basis to consider carcinogenicity protocols before the studies are initiated and final study reports when the studies are completed. A primary reviewer

from the specific reviewing division along with his or her supervisor presents the protocol or study results to the committee. In the case of a protocol for a new study, the primary reviewer assesses adequacy of proposed study design, the adequacy of the proposed doses and the selection of the transgenic mouse model if appropriate. If the committee disagrees with sponsor's proposal, the committee suggests changes such as number of animals, doses or endpoints. If committee concurs on a protocol or if changes are proposed and accepted by sponsor, the committee cannot later reject study design. In the case of final study reports, the review group also includes a biostatistician along with his or her supervisor and presents the statistical analysis of the data.

Thirty days prior to submitting a carcinogenicity protocol, the sponsor should notify the review division of their intention to submit a Special Protocol Assessment (SPA). Submission of a SPA is not a regulatory requirement; sponsors can choose to perform carcinogenicity studies without concurrence from the FDA. However, if the design, such as dose setting turns out to be flawed, FDA is not compelled to accept the studies. Supporting dose range-finding data need to be submitted prior to or with SPA. The FDA has 45 days to respond to the SPA. Once the SPA has been evaluated by the eCAC, the executive secretary will fax or email the results of the committee's deliberations to the sponsor (Carcinogenicity Study Protocol Submissions http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm078924.pdf). Concurrence must be requested prior to study initiation. If the study is performed in accordance with the eCAC recommendations, the completed study cannot be rejected based on the protocol design. If the sponsor disagrees with the eCAC their comments can be sent to the review division which will forward the inquiry to the eCAC for reconsideration. If the sponsor ignores the eCAC recommendations, it assumes the risk that a flawed design could lead to the study being rejected. There is no review clock for final study evaluations other than the PDUFA deadline for NDA review. The results of the eCAC's deliberations on final studies are not forwarded to the sponsor.

6.5 Materials to Be Included with the SPA

A 90-day toxicology study in the same rodent strain, using identical methods of administration and formulation serves to determine the maximum dose selected for the carcinogenicity bioassay as well as justifies the lower doses selected. Obviously, a 26-week study is also acceptable. For a 6-month transgenic mouse study, a 28-day dose range finding study in the wild-type strain is acceptable. Sufficient metabolism data should be submitted to demonstrate the appropriateness of the species/strain selected for covering human metabolic profile. Toxicokinetic data should enable estimation of the $AUC_{0\text{-}24}$ exposure for parent drug and any major human metabolite. Clinical exposure data at steady state for both parent and major human metabolites should be provided using the maximum recommended human dose (MRHD). Protein binding comparisons between nonclinical species and human plasma should

be provided. Also a summary of the genetic toxicology data. The API used in these studies should share the same impurity profile as will be found in the marketed drug.

6.6 Dose Selection

A critical issue in designing a carcinogenicity bioassay is the selection of the high dose. A number of metrics are available for making this determination (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Safety/S1C_R2/Step4/S1C_R2__Guideline.pdf). The most commonly used criterion is the maximum tolerated dose (MTD). The MTD can be defined using a dose that causes mortality. When this criterion is used, the MTD is generally one-third of the lethal dose. Decreases in body weight from a 6-month study or decreases body weight gain (3-month study) can serve as the basis for an MTD. Decrements of approximately 10 % compared to control are generally acceptable. Toxicities in target organs that are not compatible with long term survival can be used to set an MTD; for example liver cell necrosis, erosions in the stomach or renal tubule degeneration. For some drugs clinical signs can serve as the basis for MTD selection, for example a drug that induces seizures. Altered clinical pathology parameters can define an MTD, for example if a drug interferes with blood clotting. The magnitude of these changes must be such that the doses above that which defined the MTD would not be tolerated for the duration of the carcinogenicity study.

Pharmacokinetic parameters can also be used to set the top dose. An AUC in animals that is at least 25 fold higher than the AUC at the MRHD is acceptable. A limit dose of 1500 mg/kg can be used when the drug is used clinically at less than 500 mg/day and has a 10× AUC margin. To date, the FDA has not accepted these parameters for setting the high dose in transgenic carcinogenicity studies. None of the studies used to validate the transgenic models used criteria other than the MTD.

Saturation of absorption can also be used as the basis for a top dose since increasing the dose does not result in increased exposure. Perhaps the least desirable criterion is the maximum feasible dose. This can be acceptable provided the sponsor has shown a good faith effort to test formulations and/or routes of exposure that maximize drug exposure.

6.7 Frequently Encountered Issues

Some sponsors routinely include dual vehicle controls. This practice stems from the notion that a certain amount of “noise” is expected in a carcinogenicity study. Because of the large numbers of tissues that are examined, an apparent statistical increase in a tumor could occur by chance. Having two control groups reduces the chance of such a type 1 error. In practice, CDER biostatisticians combine the information from the two controls when comparing the drug-treated groups. In years

past, some sponsors routinely included calorie restriction as part of carcinogenicity. This was driven by the observation at animals fed ad libidum became obese, had shorter life-spans and increased tumor frequencies. This practice is rarely seen in contemporary studies.

6.8 Protocol Changes/Early Terminations

It is not uncommon that in the course of a carcinogenicity study sponsors wish to amend the protocol to change doses or to terminate groups prior to the scheduled necropsy. If a sponsor has received concurrence from the eCAC on the study protocol, the sponsor should contact the review division holding their IND or NDA to request such changes. The review division queries eCAC members to determine if such changes are appropriate. Response times to such requests are rapid, generally within 2–3 days.

Excessive mortality early in a study may result in recommendation to reduce the dose level. There are not hard and fast rules for early study termination. However, the following criteria are frequently followed. If animal survival drops to ≤20 late in the study in a manner suggesting a drug related effect, dosing may be suspended. If survival falls to 15 animals at the high dose for either males or females, after study week 100, the entire gender at all doses can be sacrificed. If the high dose in either or both sexes falls to 15 animals prior to study week 100 then just the HD group can be sacrificed and the low and mid dose can continue to the end of study.

If there are two identically treated control groups, the eCAC generally recommends combining them and if the total numbers reach 20 animals all groups of that sex can be sacrificed. If there is only one control group, all dose groups of that sex should be sacrificed once the control reaches 20 animals.

6.9 Statistical Analysis of Carcinogenicity Studies

When a carcinogenicity study is completed, the sponsor submits electronic data sets in a SAS transport file for review by statisticians at the FDA (MaPP 6610.2 Responsibilities and Procedures for Statistical Review and Evaluation of Animal Carcinogenicity Studies: http://citeseerx.ist.psu.edu/viewdoc/download;jsessionid=74700B0F1B43370E4D97B07BFD921D50?doi=10.1.1.174.1708&rep=rep1&type=pdf). Such reviews include standard assessments as well as special evaluations/combinations requested by nonclinical reviewer or eCAC. The results from this report are incorporated into the nonclinical review and presented jointly to eCAC for final adjudication.

In performing statistical analyses certain tumors should be grouped across tissues, e.g. lymphoreticular and hematopoietic neoplasms. Other tumors should be combined within organs, e.g. hepatic adenoma and carcinomas [36]. To be

considered statistically significant an increase in tumors must be positive by both the trend test and by pairwise analysis. Different p-values are employed for common versus rare tumors. Common tumors are those seen with a frequency greater than 1 % in historical control data. To be considered a significant increase a p-value of <0.01 must be reached for pairwise comparison and a p-value of <0.005 for the trend test. Rare tumors are those seen with a frequency of less than <1 % in historical control data. To be considered a significant increase a p-value of <0.05 must be reached for pairwise comparison and <0.025 for the trend test.

The outcome of carcinogenicity studies is rarely an approvability issue. Positive results are included in the drug label under the section labeled *Carcinogenesis*, *mutagenesis*, *impairment of fertility*. This section describes the types of tumors seen and exposure margins relative to clinical exposures. If there is a serious concern for potential carcinogenicity, the results can be described in a "black box warning" at the top of the label. Some tumors are considered to have equivocal or limited relevance for human risk evaluation. For example, hepatic and/or thyroid tumors can be caused by drug-induced of enzyme induction. Leydig cell tumors can result from drug-induced increases in luteinizing hormone, Dopamine antagonist blockers can result in prolactin-mediated tumors of mammary, pituitary, and endocrine pancreas. These types of tumors are still included in the label but often with the caveat that their relevance to human risk is unknown.

6.10 Full CAC Meeting

The full CAC is comprised of all pharmacology/toxicology supervisors in the Office of New Drugs, approximately 25 individuals. The full CAC meets only on rare occasions to deal with unusual issues. For example, if the eCAC fails to agree on the outcome of a carcinogenicity study the full CAC would convene to render an opinion. On a few occasions, sponsors have disagreed with eCAC conclusions and requested to present their interpretation to the full CAC. A reviewer or supervisor from the regulating division would present the agency's viewpoint followed by the sponsor. The full CAC would discuss the issue and vote on the interpretation of the data. The sponsor is not present during this discussion on the subsequent vote.

6.11 The Path Forward

With our current understanding of the carcinogenic process and how chemicals produce tumors, there is growing awareness that a single study or group of studies is unlikely to provide a sufficiently robust data set for human risk assessment. Pharmaceutical chemicals provide a particularly difficult challenge as they are designed to produce a pharmacological effect. As such, simple in vitro or in vivo

test systems are likely to show effects produced by these agents. The challenge remains understanding the significance of these findings for human risk.

Some attempts have been made to supplant or augment animal testing with in silico predictive tools using either statistical quantitative structure-activity relationships (QSAR approaches) or rule-based expert systems such as Multicase [11]. While remaining of potential interest at least in early screening, the training datasets for these tools remain insufficiently comprehensive and robust to offer sufficient predictive value at the present time. Another approach that is very early in its development but that shows intriguing promise is a transcriptomic approach to identification of signals of concern for carcinogenicity [51]. As more experience is gained with techniques like this with powerful computational support, additional important information may be offered that can be used to detect compounds that warrant further study.

Over the last 10–15 years, there has been an increasing awareness of the need for a global evaluation of all of the available data to enable an appropriate assessment of human risk of cancer from chemical exposure and several alternative integrative approaches have been proposed [9, 12, 22, 34]. As will be discussed in subsequent chapters of this book, a critical component of this assessment is a determination of the potential of the chemical to cause genetic toxicity. The assessment of toxic potential of new pharmaceutical agents involves a series of studies in vitro and in vivo designed to understand how to test the therapeutic efficacy of novel compounds safely in humans. In addition to the in vitro and in vivo genetic toxicity studies (discussed elsewhere in this book), a battery of studies in rodent and non-rodent species up to 6 months in rodents and 9–12 months in non-rodents generate a large body of data that can be incorporated into this global weight-of-evidence approach to assessment of carcinogenic potential. There is growing awareness that important information on pre-neoplastic events can be obtained from these studies and that data from the 2 year bioassays may not be as critical as originally thought for assessment of human risk of cancer [26].

If one examines the known human carcinogenic pharmaceuticals, it can be seen that these chemicals are either genetic toxins, immunosuppressants, or endocrine stimulants (with the exception of topically applied arsenicals) [43]. It has been suggested that histologic data from chronic toxicity studies (both in rodents and non-rodents) along with data that will inform these pharmacodynamic activities (in vitro and genetic toxicity data, in vitro and in vivo pharmacological data) can provide sufficient information to reliably predict human carcinogenic risk. A cross-industry retrospective study evaluated the predictive capability of data from chronic toxicity studies and, using this information, made a proposal for a tiered approach employing 2 year rodent studies only in those cases where decisions could not be made from the available data or questions still persisted [47]. This proposal has formed the basis for an ongoing prospective study that will inform discussions on the current ICH S1 guidance on rodent carcinogenicity assessment [44]. In this effort, companies will submit voluntary dossiers on the carcinogenic potential of their novel molecules ahead of the conduct of the 2 year studies predicting the expected outcome of these studies and assessing whether a 2 year study would alter the human carcinogenic

risk assessment. If the data from this study support the conclusions from the retrospective evaluation, it may enable an alteration of the current global regulatory guidelines requiring a standard rodent bioassay for each new chemical entity. The proposal under consideration would restrict the rodent bioassay for those cases where it was not possible to obtain definitive data from in vitro and chronic in vivo assays on the carcinogenic potential of new pharmaceutical agents.

The rodent bioassay was conceived and implemented at a time when comparatively very little was understood about the carcinogenic process or how chemicals might produce human cancer. At the time of the inception of this approach, this bioassay represented the best thinking on how to address the critical challenge posed by the understanding that chemicals do, indeed, possess the potential to cause cancer and it was important to address this risk before widespread exposure to novel agents. The 60 years since this assay was first proposed and used have seen an evolution of thinking based on important advances in the sciences. The modifications to how we address this important challenge that are coming into practice and are under consideration would seem to be an appropriate direction and offer the promise of improving our ability to predict human cancer risks with streamlined processes that reflect our growing knowledge in this challenging area.

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