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Comparative Pathobiology of Environmentally Induced Lung Cancers in Humans and Rodents

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Abstract

Lung cancer is the number one cause of cancer-related deaths in humans worldwide. Environmental factors play an important role in the epidemiology of these cancers. Rodents are the most common experimental model to study human lung cancers and are frequently used in bioassays to identify environmental exposure hazards associated with lung cancer. Lung tumors in rodents are common, particularly in certain strains of mice. Rodent lung tumors are predominantly bronchioloalveolar carcinomas and usually follow a progressive continuum of hyperplasia to adenoma to carcinoma. Human lung cancers are phenotypically more diverse and broadly constitute 2 types: small cell lung cancers or non-small cell lung cancers. Rodent lung tumors resulting from exposure to environmental agents are comparable to certain adenocarcinomas that are a subset of human non-small cell lung cancers. Human pulmonary carcinomas differ from rodent lung tumors by exhibiting greater morphologic heterogeneity (encompassing squamous cell, neuroendocrine, mucinous, sarcomatoid, and multiple cell combinations), higher metastatic rate, higher stromal response, aggressive clinical behavior, and lack of a clear continuum of proliferative lesions. In spite of these differences, rodent lung tumors recapitulate several fundamental aspects of human lung tumor biology at the morphologic and molecular level especially in lung cancers resulting from exposure to environmental carcinogens.

Keywords

lung cancer; animal models; environmental carcinogens; comparative pathology

Introduction

> “If an experiment yields a clear-cut negative result, there is little discussion about the meaning or the meaninglessness of animal studies. When a clear-cut and strong positive result occurs, there is also little discussion. When the result is a slightly positive experiment, interpretation becomes difficult and discussion becomes lengthy. Biology, unfortunately, does not come only in black and white, but in many shades of gray, and in these grey areas disagreement is particularly evident” - David Rall, 1988

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The above quote from Dr. David Rall, a pioneer and leader in environmental health sciences, is very germane when comparing rodent models to human diseases including lung cancer from environmental exposures (Rall, 1988, Huff, 1999). The goal of this brief review was to present pros and cons on the suitability of rodent models to study environmentally induced human lung cancers. Of course, as Dr. Rall suggested, we are all well aware that the issue of suitability of the rodent models to study environmentally induced lung cancers in humans is not black or white but has a gray scale spectrum. This mainly depends on the nature of exposures and on the unique biology of rodent species that differs from humans in certain aspects but is also similar in many ways.

Epidemiological studies provide direct information about potential associations between an environmental challenge and the risk of human cancer. However, there are several limitations for these studies, such as availability of suitable cohorts, long latency of cancer, limitations in the strength of causal inferences, poorly defined exposures, and several other biases (Cogliano *et al.*, 2004). Epidemiological studies are very important in making unexpected and often logic defying associations of potential environmental exposures and human disease but in order to determine causality between these exposures and disease, animal studies involving chronic exposure to the environmental challenge are indispensable. However, cancer bioassays also have some limitations associated with methods of exposure, complex mixtures, limited genetic variation, and species-specific metabolism differences. Nonetheless, animal studies are essential for hazard identification and risk assessment of environmental exposures (Huff, 1999).

In this paper, I will discuss some of the similarities and differences between human and rodent lung tumors as well as some issues related to the value of rodent models (rats and mice) for studying environmentally induced lung cancers.

Brief overview on the comparative pathobiology of rodent and human lung tumors

Lung cancer is the number one cause of cancer-related deaths in humans worldwide. In the United States, lung cancer incidence is comparable to the combined cancer related deaths resulting from the cancers of breast, pancreas, prostate, and colon and rectum (USCSWG, 2013). The majority (~85%) of the lung cancer related deaths are due to tobacco smoking; however, a significant number of lung cancer related deaths are due to occupational or environmental exposures, such as radon, asbestos, crystalline silica, mixtures of polycyclic aromatic hydrocarbons, heavy metals, and air pollution (Travis *et al.*, 1999). In recent times, due to a significant decrease in tobacco smoking, there is a corresponding decrease in the incidence of lung cancer. However, there is no decrease in lung cancer related deaths due to factors other than smoking.

Lung tumors in rodents and humans are classified based on different criteria. Rodent lung tumors are primarily classified based on their cellular origin and/or location within the airways, where as human lung tumors are primarily classified based on more descriptive morphologic features with prognostic value (Nikitin *et al.*, 2004). As a result, as discussed below, the rodent and human histologic terminology cannot be used interchangeably.

Lung cancers in humans are usually divided into two major groups: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) (Travis *et al.*, 2011). NSCLC includes all epithelial lung cancers other than SCLC, most of which exhibit neuroendocrine morphology and markers. NSCLC comprise 80% of all lung tumors and have a variety of morphologies that include adenocarcinomas, squamous cell carcinomas, adenosquamous carcinomas, large cell carcinomas, and sarcomatoid carcinomas. Adenocarcinomas account for 30-40% of lung cancers and often arise in peripheral regions of the lung and may have a lepidic (neoplastic cells lining the alveolar walls), acinar, papillary, micropapillary, solid and several other variants including invasive mucinous, colloid, fetal and enteric morphologies (Travis *et al.*, 2011). Squamous cell carcinomas constitute 20-25% of all lung cancers and arise centrally within large bronchi and have largely been associated with tobacco smoking. Large cell carcinomas account for 15-20% and occur diffusely in the lung and are characterized by large cells with large nuclei and prominent nucleoli and lack of glandular or squamous differentiation (Tuveson and Jacks, 1999). About 18% of lung tumors may be categorized as SCLC that have a neuroendocrine morphology and a very high metastatic potential. The remaining 2% are neuroendocrine tumors consisting of typical and atypical carcinoids (Meuwissen and Berns, 2005).

According to the recent classification of the human lung adenocarcinomas by the International Association for the Study of Lung Cancer/American Thoracic Society/ European Respiratory Society, the term bronchioloalveolar carcinoma is no longer used for resected lung specimens. In its place, new terms for small solitary adenocarcinomas have been proposed: adenocarcinoma *in situ* (AIS) with pure lepidic growth and no invasion, minimally invasive adenocarcinoma (MIA) with predominant lepidic growth and with < 5 mm invasion, and lepidic predominant adenocarcinoma (LPA) with > 5mm invasion (Travis *et al.*, 2011). The term bronchioloalveolar carcinoma used in rodents is not equivalent to the human lesion (Nikitin *et al.*, 2004). Human lung cancer has a high degree of histological heterogeneity within each tumor mass and may contain glandular, squamous, and neuroendocrine components, and the commonly diagnosed “mixed” subtype accounts for more than 90% of all resected lung adenocarcinomas. The recent classification also recommended not using the term mixed subtype and instead recommended classifying these invasive adenocarcinomas based on the predominant histologic pattern such as lepidic, acinar, papillary, micropapillary and solid (Travis *et al.*, 2011). Other differences between rodent and human lung tumors include greater stromal response and higher metastatic rates in human lung tumors compared to mouse lung tumors. The rodent lung tumors, especially the chemically induced tumors, have higher tumor multiplicity than human lung cancers (Nikitin *et al.*, 2004).

On the contrary, the rodent lung tumors are predominantly of a single histological type (Dixon *et al.*, 1999, Boorman and Eustis, 1990). The most commonly occurring lung tumors in rodents are termed bronchioloalveolar adenomas or carcinomas (Boorman and Eustis, 1990, Dixon *et al.*, 1999, Renne *et al.*, 2009). This terminology is used in rodent lung tumors to primarily account for the location (bronchiolar alveolar region) of the tumors and the cell of origin (type II pneumocytes or Clara (club) cells) and is not typically comparable to the human lesion bearing the same name as described above (Nikitin *et al.*, 2004). The

histological heterogeneity of the rodent bronchioloalveolar tumors is very limited comparable to the human adenocarcinomas. The bronchioloalveolar tumors in rodents may be seen in vehicle control or chemically treated groups. However, other types of lung tumors such as cystic keratinizing epitheliomas and squamous cell carcinomas in rodents are observed with certain chemical inhalation exposures such as dioxin (TCDD) and particulates (Titanium dioxide, Talc, Nickel oxide) but not in unexposed control rodents (Dixon *et al.*, 2008). Pulmonary neuroendocrine tumors (similar to SCLC in humans) that account for a significant number (~20%) of tumors in tobacco smokers have not been reported in rodents (Nikitin *et al.*, 2004).

Lung tumors in rats and mice originate primarily in peripheral lung involving the distal bronchioles and alveolar acini, and bronchial or proximal bronchiolar tumors are very rare. There is a well-documented and accepted paradigm of progression of the rodent lung tumors in the form of a continuum: hyperplasia to adenoma to carcinoma. In spite of the use of diagnoses of pre-invasive lesions such as AIS and MIA, the progression of human lung adenocarcinomas from the pre-invasive stage to malignancy is poorly understood. However, the lesion that was designated as atypical adenomatous hyperplasia in humans bears histological similarities to alveolar hyperplasia in rodents, and is thought to be a precursor lesion for peripheral lung adenocarcinomas. The term adenoma is reserved for only a few select, uncommon human lung tumors.

The chronic rodent (rat and mouse) bioassay is the standard test to assess carcinogenicity of environmental agents suspected of causing cancers in humans (Cogliano, 2006). There are species, strain and sex differences in the incidence of lung tumors in rodents (Boorman and Eustis, 1990, Dixon *et al.*, 1999). The rodent male has a higher lung tumor incidence than the female. Mice have higher incidences of spontaneous and chemically induced proliferative lung lesions (hyperplasia, adenoma and carcinoma) than rats (Boorman and Eustis, 1990, Dixon *et al.*, 1999). There are strain differences in both species. In mice, the incidence of spontaneous lung tumors is strain dependent and the incidence of chemically induced lung tumors also follows the same strain dependency (Malkinson, 2001). The order of decreasing incidences of spontaneous lung tumors in mice is A/J (82%) > SWR/J (47%) > BALB/c (33%) > CBA (17%) > C3H (9%) > C57BL6 (3%) (Manenti and Dragani, 2005). The higher lung tumor susceptibility of mice is due to the pulmonary adenoma susceptibility 1 (*Pas1*) locus and the differential lung tumor susceptibility of various mouse strains has been attributed to *Pas1* locus polymorphisms that can be of either an A/J- or C57BL/6J-type *Pas1* haplotypes. The A/J-type haplotype has a higher spontaneous lung tumor incidence than the C57BL/6J-type haplotype. The National Toxicology Program's mouse model (B6C3F1) has the C57BL/6J-type haplotype since both the parent C57BL6 and C3H strains have the C57BL/6J-type haplotype (Manenti and Dragani, 2005). The incidence of spontaneous lung tumors in male and female B6C3F1 mice is 27.7% and 9.5% (n=950/sex; (NTP, 2013). The strain differences in the incidence of spontaneous lung tumors in the rat are not as striking as in the mouse. The order of decreasing incidences of spontaneous lung tumors in various rat strains is F344 (1.9%), Lewis (1.8%) > Osborne Mendel (0.7%), Brown Norway (0.6%) > Sprague Dawley (0.5%), Wistar (0.5%), CD (0.4%) > ACI/N (0%) (Manenti and Dragani, 2005). The status of *Pas1* locus in various rat strains needs to be

determined. The incidence of spontaneous lung tumors in male and female F344 rats is 3.6% and 1.4%, respectively (n=700/sex; (NTP, 2013).

Lung cancer of rodents and humans shares several important morphologic and molecular similarities (Nikitin *et al.*, 2004, Malkinson, 2001). The bronchioloalveolar tumors in rodents are very similar to the human non-small cell carcinomas, adenocarcinoma subtype. The majority of the human lung tumors are due to tobacco smoke and the tobacco smoke induced lung tumors are primarily bronchial or central in origin and are predominantly squamous cell carcinomas or small cell carcinomas (Travis *et al.*, 1999). However, a significant decrease in tobacco smoking, or cessation of smoking, improved diagnosis, and use of filtered cigarettes appear to have resulted in alterations in the incidences and types of lung tumors in humans. As a result of the above factors, there is a reduction in the incidences of bronchial squamous cell carcinomas and small cell carcinomas and an increase in the incidences of adenocarcinomas (Devesa *et al.*, 2005). Interestingly, cessation of smoking in previous smokers results in a decrease in the incidences of bronchial squamous cell carcinomas and small cell carcinomas but not adenocarcinomas (Khuder and Mutgi, 2001, Jedrychowski *et al.*, 1992). Better imaging technologies and diagnostic tests have also contributed to the higher diagnoses of adenocarcinomas.

There is a significant increase in the incidence of peripheral pulmonary adenocarcinomas in non-smokers, women and Asians (Devesa *et al.*, 2005, Scagliotti *et al.*, 2009). Since the rodent lung tumors are predominantly adenocarcinomas with comparable morphology to human adenocarcinomas (papillary, acinar, solid), they are more relevant for the study of environmentally induced lung cancers. This is particularly relevant in the majority of the population that doesn't smoke but still is exposed to environmental carcinogens.

The KRAS gene is commonly altered in human and rodent lung tumors (Wakamatsu *et al.*, 2007). The *KRAS* mutations in humans are primarily targeted within codon 12 followed by codons 61 and 13 and the same trend is seen in mouse tumors. The predominant *KRAS* mutation in pulmonary adenocarcinomas in non-smokers and spontaneously arising bronchioloalveolar carcinomas in mice is a G to A transition. Interestingly, the pulmonary adenocarcinomas in smokers and chemically induced bronchioloalveolar carcinomas in mice usually harbor G to T transversions (Husgafvel-Pursiainen and Kannio, 1996, Hong *et al.*, 2007, Hong *et al.*, 2008, Riely *et al.*, 2008, Sills *et al.*, 1999). Meta-analysis of transcriptomic alterations in human and mouse lung tumors revealed significant similarities in lung cancer pathways in both species (Stearman *et al.*, 2005, Bonner *et al.*, 2004, Pandiri *et al.*, 2012). These data indicate that mouse lung tumors are similar to human adenocarcinomas at the morphologic and molecular levels and that mouse lung tumors are relevant in evaluating carcinogenic hazards associated with environmental exposures.

It is pertinent to note that rodents played a very important role in detecting environmental carcinogens even before epidemiologic studies suspected any association of these agents with human cancer. Examples include asbestos, beryllium, cadmium, 1,3 butadiene, bis(chloromethyl) ether, ethylene oxide, glass wool, sulfur mustard, radon gas, crystalline silica, vinyl chloride and 2,3,7,8-TCDD. In a recent workshop organized by the US EPA on mouse lung tumors, Dr. Dan Krewski from the University of Ottawa presented information

on the human and rodent cancer site concordance of IARC group I agents (109) (Krewski, 2014). Tumors in the lung had greater site concordance than any other organ in the body, indicating that rodents are indeed most suitable to study environmental pulmonary carcinogens. Not surprisingly, the majority (~ 73%) of these 109 IARC group I agents are genotoxic carcinogens. However, this list also includes a significant number (~27%) of non-genotoxic carcinogens (Hernandez *et al.*, 2009).

In subsequent sections, I will discuss some limitations of using rodent models, especially the mouse, in evaluating suspected non-genotoxic (or genotoxic via the metabolites) pulmonary carcinogens.

Examples of clear human carcinogens that were difficult to model in rodents

There is overwhelming epidemiologic data demonstrating the lung cancer hazard associated with exposures to arsenic and tobacco smoke. In fact, arsenic and tobacco smoke are IARC group I carcinogens that cause human lung cancer. However, unequivocal demonstration of lung cancer hazard using rodent models has proved elusive for a long time.

Arsenic and inorganic arsenic compounds have long been considered a conundrum in the field of chemically induced carcinogenesis. The first IARC monograph (1973) indicated that inorganic arsenic exposure was consistently linked to human skin cancer but supporting animal carcinogenicity data was lacking (IARC, 1973). The 1987 IARC document indicated that the evidence of carcinogenicity of arsenic in rodents was inadequate or limited (IARC, 1987). Since the 1990s, there is an increasing accumulation of data demonstrating the carcinogenicity of arsenic in rodents but even in the recent past, arsenic was considered a paradoxical carcinogen due to lack of unequivocal carcinogenicity in common lab animal models (NSF, 2005). In a recent review on the topic, Tokar et al., 2010 noted that arsenic carcinogenicity has been demonstrated in rodents exposed to arsenic transplacentally and whole-life, or in rodent models that were predisposed to cancer, which are not common protocols in the chronic rodent bioassays (Tokar *et al.*, 2010, Waalkes *et al.*, 2004, Hayashi *et al.*, 1998). In addition, recently Waalkes and colleagues at NIEHS have demonstrated lung tumor induction in the CD1 mouse by whole-life exposure to sodium arsenite (50 ppb) at very low doses (in parts per billion) that are relevant at environmental exposure levels (Waalkes *et al.*, 2014). In light of all these data, considering arsenic as a paradoxical carcinogen is no longer tenable or warranted (IARC, 2012a).

Tobacco smoke is a known human carcinogen but it was difficult to model pulmonary carcinogenesis in rodent models using tobacco smoke. Tobacco smoke is a complex mixture with more than 5300 compounds, of which more than 70 constituents have been shown to have sufficient evidence of carcinogenicity in either lab animals or humans (IARC, 2004). Tobacco smoke has been recognized as a cause of human lung cancer since the 1940s but the unequivocal demonstration of lung tumors in rodents has been not very successful (Lorenz, 1943, Otto and Elmenhorst, 1967, Harris and Negroni, 1967). Some of the early studies may have been limited by using mouse strains with high background spontaneous lung tumor incidence and lack of sufficient challenge exposures. However, protocols involving lifetime exposures in C57BL6 mice (Harris *et al.*, 1974), Snell's mice (Leuchtenberger and Leuchtenberger, 1970) and B6C3F1 mice (Hutt *et al.*, 2005) have

resulted in a significant increase in lung tumors. Whole body exposure of Swiss albino mice to tobacco smoke within 12 hours of birth for 120 days have resulted in lung tumors (Balansky *et al.*, 2007). Witschi and colleagues used an unconventional protocol of 5 month tobacco smoke exposure followed by a 4 month recovery period in air and found increases in lung tumor multiplicities compared to controls using Balb/c, SWR and AJ mice (Witschi *et al.*, 2002). Tobacco smoke exposure studies in rats were also not uniformly positive. Lifetime exposure of tobacco smoke to Wistar rats did not increase lung tumor incidence (Davis *et al.*, 1975). However, lifetime tobacco smoke exposure of F344 rats (Dalbey *et al.*, 1980, Mauderly *et al.*, 2004) and CDF rats (Finch *et al.*, 1995) resulted in an increase in lung tumor incidence. Thus, life time, perinatal exposure or certain exposure protocols of rodents to tobacco smoke results in pulmonary adenomas and carcinomas and the idea that tobacco smoke carcinogenesis cannot be replicated in rodents is not warranted (IARC, 2012c).

Examples of chemicals that are pulmonary carcinogens in only one species

In a survey of 580 NTP chronic bioassays, there were only 67 bioassays where the same chemical was tested in both mice and rats and at least one species had a lung tumor response. Of these 67 bioassays, only 14 (21%) had lung tumor site concordance for both rats and mice. It shows that there is no absolute site concordance for lung (or for any other organ) in both rat and mouse chronic bioassays. Chemically induced lung tumor incidence in the mouse is slightly more than twice that observed in the rat (Table 1). Chemicals such as styrene, naphthalene, coumarin, ethylbenzene, cumene, and benzofuran are pulmonary carcinogens only in the mouse but not in the rat (NTP, 1979, NTP, 1992, Chan, 1992, NTP, 1993, NTP, 1999, NTP, 2009, NTP, 1989). With the exception of styrene, all these chemicals are carcinogenic in both rats and mice but interestingly the lung tumors were observed only in mice but not in rats. The unique species specificity of the mouse at least to styrene is mainly due to the unique CYP isoform CYP2F2 in the mouse Clara (club) cells compared to CYP2F4 in rats and CYP2F1 in humans. CYP2F2 is highly efficient in metabolizing styrene to styrene 7,8-oxide (SO) and other metabolites. These metabolites are cytotoxic to Clara cells and cause regenerative hyperplasia and subsequently result in proliferative lung lesions including neoplasia (Cruzan *et al.*, 2009). On the other hand, styrene is also metabolized by CYP2E1 in the liver in rats, mice and humans resulting in the formation of SO and other metabolites that needs further characterization. In addition, occupational exposure to styrene leads to formation of O6-deoxyguanosine (O6-(2-hydroxy-1-phenylethyl)-2′-deoxyguanosine-3′-monophosphate) and N7-deoxyguanosine adducts in DNA. Low levels of these two adducts were also detected in liver of mice and rats exposed to styrene. Thus even though there is no site concordance of styrene-induced mouse lung tumors with rats and humans, the presence of the DNA adducts, chromosomal damage and some common metabolites that are genotoxic is of concern. As a result, IARC considers styrene as probably carcinogenic (group 2B) to humans, and the NTP Report on Carcinogens considers styrene to be reasonably anticipated to be a human carcinogen (NTP, 2011, IARC, 2002, NRC, 2014).

Relevance of cancer site concordance in risk assessment

The rodent bioassays are typically used as screens to identify hazards associated with chemical carcinogenesis. As discussed earlier, there is carcinogenicity site concordance for some organs more than others. However, an important issue that is repeatedly raised is the question if site concordance is really necessary to identify a carcinogenic hazard. According to the EPA guidelines for carcinogen risk assessment, cancer site concordance is not always assumed between animals and humans since at the cellular level, growth control mechanisms are homologous among mammals and cancer site concordance is not always observed with chemicals that are carcinogenic in both humans and animals (EPA, 2005). For example, vinyl chloride and benzene are carcinogenic to both humans and animals but cancer site concordance is seen only with vinyl chloride but not benzene (NRC, 1994). In addition, the recent decision by the IARC to consider the use of mechanistic data in the absence of sufficient data on human carcinogenicity implies that site concordance is not essential to identify a carcinogenic hazard (Cogliano *et al.*, 2008). The underlying premise for this decision is that certain mechanisms of action of chemical carcinogenesis are conserved across species and that cancer site concordance is not really necessary as long as the common plausible mechanism of action is demonstrated in both species. A classic example for this is the aryl hydrocarbon receptor (AhR) signaling by dioxin and dioxin-like chemicals that results in changes in gene expression resulting in alterations in cell replication and apoptosis, causing tumors in a variety of organs in both species (NTP, 2006). TCDD (2,3,7,8-tetrachlorodibenzo-*para*-dioxin) is one such chemical that was classified as group I carcinogen based on sufficient evidence of carcinogenicity in experimental animals and strong mechanistic data based on AhR activation. Similarly 2,3,4,7,8-pentachlorodibenzofuran and 3,3′,4,4′,5-pentachlorobiphenyl (PCB 126) are complete carcinogens (capable of initiation and promotion of carcinogenesis) in experimental animals, and there is ample evidence that they act through the same AhR-mediated mechanism and hence were classified as group I carcinogens by IARC (Cogliano *et al.*, 2008).

On some occasions, there may be multiple modes of action influencing the apical outcomes and/or conflicting data published on human relevance of a particular rodent carcinogen (Bond *et al.*, 1995, Melnick and Kohn, 1995). A good example of conflicting data on the human relevance of 1,3-butadiene induced carcinogenicity are publications by Bond et al., 1995 and Melnick and Kohn, 1995, where the former concluded that 1,3-butadiene will not be carcinogenic to humans at occupational exposure levels while the latter concluded that it is carcinogenic (Cogliano *et al.*, 2004). 1,3-butadiene is considered a group I carcinogen and causes cancer of the hemolymphatic organs in humans and is also a multi-site carcinogen in experimental animals. There is clear evidence of carcinogenicity in both rats and mice but there was little tumor site concordance between the species. In mice, there was evidence of carcinogenicity within the hematopoietic system, circulatory system, lung, liver, forestomach, Harderian gland, preputial gland, and mammary gland, while in rats there was evidence of carcinogenicity in mammary gland and possibly the brain, thyroid, testis, uterus, Zymbal’s gland and kidney (Melnick and Sills, 2001, Melnick *et al.*, 1999).

Another point to keep in mind regarding the cancer site concordance between humans and rodents is the limitations of the existing epidemiological studies. 1,3-butadiene-induced

mammary tumors were noted in both rats and mice but there was no epidemiologic evidence supporting breast cancer risk in humans since all the people included in the epidemiologic studies were men in the industrial setting (IARC, 2012b). Some epidemiologic studies have just started exploring the link between 1,3-butadiene exposure and breast cancer (IARC).

The above examples demonstrate that a thorough examination of the epidemiologic data and the multiple modes of action of a chemical should be explored before making conclusive decisions on human relevance of chemical-induced tumors in animals.

Concluding remarks

In general, there is good agreement between lung tumors in rodent bioassays and human lung cancer hazard due to environmental pulmonary carcinogens. The exceptions and controversies of disagreement between mouse lung tumors and human pulmonary carcinogenic hazard are usually centered on the mouse Clara (club) cell biology. Unlike the rat, the mouse is especially sensitive to a large number of metabolically activated pulmonary toxicants. Mice have higher numbers of Clara cells than humans, throughout the large and small airways. Species-specific qualitative and quantitative differences in CYP isoforms and their respective metabolizing abilities result in species-specific pulmonary toxicity and possibly neoplasia. Clara cells of mice have the CYP2F2 enzyme that plays a major role in producing toxic metabolites more efficiently than other related CYP isoforms such as CYP2F1 in humans and CYP2F4 in rats. Chemicals that mediate pulmonary toxicity and subsequent neoplasia in mice include styrene, naphthalene, coumarin, 3-methylindole (via CYP2F2 mechanism (Carlson, 1997, Buckpitt *et al.*, 1995, Born *et al.*, 2002), 4-ipomeanol (via CYP4B1) (Czerwinski *et al.*, 1991), 1,1-dichloroethylene (via CYP2E1, CYP2F2) and trichloroethylene (via CYP2E1) (Odum *et al.*, 1992). There is a great diversity of oxidative enzymes expressed in lungs of various species including humans. In human lungs, various CYPs that are expressed include 1A1 (only in smokers), 1B1, 2A13, 2B6, 2C9, 2D6, 2E1, 2F1, 2J2, 2S1, 3A4, 3A5, and 4B1 (Bernauer *et al.*, 2006, Hukkanen *et al.*, 2002, Zhang *et al.*, 2006). Similarly, rodent lungs also express as many different CYPs with several qualitative and quantitative differences. Thus, there is no unequivocal standard for the risk assessment of pulmonary carcinogenicity in rodents and its relevance to human disease.

The immunohistochemical staining of chemically induced lung tumors in rodents is typically positive for type II pneumocyte markers (SPC) and to a lesser extent positive for Clara (club) cell markers (CC10). Some recent publications suggest that the cell of origin in KRAS driven mouse lung tumors is a type II pneumocyte (Mainardi *et al.*, 2014, Sutherland *et al.*, 2014, Xu *et al.*, 2012). However, the question of cell of origin in chemically induced pulmonary carcinogenesis needs to be resolved. This information is particularly relevant since Clara cell cytotoxicity and subsequent hyperplasia and neoplasia is the proposed mode of action of several pulmonary carcinogens in the mouse (Cruzan *et al.*, 2009). On the other hand, it is has been hypothesized that regenerating Clara cells may lose their CC10 expression and transdifferentiate into other cell types (Rawlins and Hogan, 2006). Thus, immunohistochemical staining of tumors collected at terminal sacrifice may not provide an answer to the cell of origin of chemically induced lung tumors. Approaches such as cell lineage tracing experiments, as well as other investigative studies, are needed to understand

the cell of origin in chemically induced pulmonary carcinogenesis that might give an insight into the mode of action.

Several issues that need to be resolved when evaluating the relevance of rodent lung tumors for human risk assessment include issues related to epidemiologic evidence in susceptible populations and life stages, exposure paradigms, species differences in tissue dosimetry, toxicokinetic data, mechanistic data, definitive characterization of species specific phase I and II metabolizing enzymes and the resulting metabolites, threshold issues, etc. In spite of these unresolved issues, it is likely that the use of laboratory rodents in bioassays will continue to provide important information for hazard identification, as well as an insight into the mechanisms of chemically induced pulmonary carcinogenesis.

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Table 1

Species differences in chemically induced lung tumor response (with clear or some evidence of carcinogenicity) in NTP chronic bioassays*

Animal species and sex	Studies that are carcinogenic including all organs, n=67; %(n)	Studies with lung tumor response, n=67; %(n)
Rat Male	69% (46)	24% (16)
Rat Female	70% (47)	24% (16)
Mouse Male	63% (42)	60% (40)
Mouse Female	76% (51)	64% (43)

*In a survey of 580 NTP chronic bioassays, there were only 67 studies where the same chemical was tested in both mice and rats and at least one species had a lung tumor response.