【药物非临床毒性病理学评价】

致癌试验与人类风险评估无关的肿瘤概述

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摘 要：致癌试验的目的是考察药物在动物体内的潜在致癌作用，从而评价其可能对人类的相关风险，是非临床药物安全性评价的主要内容之一。啮齿动物致癌试验的结果与人类安全性评估的相关性经常引起争议，可能需要做进一步的研究来探讨其作用方式，以帮助确定是否存在对人类的潜在致癌性。当啮齿动物致癌试验出现阳性结果时，可能需要进行进一步的毒性病理学研究探讨其作用机制，来评估与人类的相关性。简要介绍动物致癌试验结果与人类相关性的必要性、致癌试验基于作用方式与人类风险评估无关的肿瘤、致癌试验基于作用方式与人类风险评估可能无关的肿瘤，以期为我国非临床药物致癌试验的结果分析和药物评价研究提供一定参考。

关键词：致癌试验；非临床药物安全性评价；毒性病理学；作用方式；风险评估
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Overview of tumors of carcinogenicity studies irrelevant to risk assessment of humans

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Abstract: The objective of carcinogenicity study is to identify the potential carcinogenesis in animals and to assess the relevant risks in humans of drugs, which is one of the major components of nonclinical safety evaluation of drugs. The relevance between the results of rodent carcinogenicity studies and assessment of human safety are often the cause for debate. Further toxicologic pathology research may be needed to investigate the mode of action, which contribute to confirm the presence or the lack of potential carcinogenesis for humans. When rodent carcinogenicity study shows positive results, further studies may be needed to investigate the mechanism of action to assess the correlation with humans. This article gives brief introduction of the need for evaluating the relevance between study results in animals and human safety in carcinogenicity study, some tumors in carcinogenicity study not relevant to humans, some tumors in carcinogenicity study possibly not relevant to humans based on mode of action, in order to provide some references for the result analysis of nonclinical carcinogenicity study and drug evaluation research in China.

Key words: carcinogenicity study; nonclinical safety evaluation of drugs; toxicologic pathology; mode of action; risk assessment

癌症严重威胁人类的健康和生命，在世界上许多国家和地区，癌症都是导致人类死亡的主要原因，目前人类80%以上的癌症都与环境因素相关，而其中的主要因素是化学物质[1]。化学物质可分为遗传毒性化学物质、表观遗传性化学物质和未分类3种。遗传毒性化学物质具有明确的DNA反应性，具有多靶点、潜伏期短、多种属反应性等特点，肿瘤的增加往往强烈暗示对人类的潜在危害；表观遗传

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性化学物质不直接产生DNA损伤，其致癌作用机制具有典型的物种、性别和组织特异性，可能只在特定的啮齿动物或仅在极高剂量下出现潜在致瘤作用，这些影响要么被认为与人类危害无关，要么可以进行阈值暴露的风险评估来判断对人类的危害性。

药物研发中筛选出的候选药物在进入临床试验前，首先需要进行良好实验室规范（good laboratory practice，GLP）条件下的非临床安全性研究对其潜在毒性进行评价，其中致癌试验是药物非临床安全性评价的主要内容之一，其目的是考察药物在动物体内的潜在致癌作用，从而评价和预测其可能对人体造成的危害。从1995年起，国际人用药品注册技术要求协调会（International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use，ICH）、经济合作与发展组织（Organization for Economic Co-operation and Development，OECD）、美国环境保护署（Environmental Protection Agency，EPA）、美国食品药品监督管理局（Food and Drug Administration，FDA）、中国国家药品监督管理局（National Medical Products Administration，NMPA）（原CFDA）等国内外机构陆续公布了《S1A，S1B，S1C，S1D》[2]、《化学品测试指南：致癌性研究》[3]、《致癌性健康影响测试指南（OPPTS 870.4200）》[4]、《红皮书2000：第IV.C.6章，啮齿动物致癌性研究》[5]和《药物致癌试验必要性的技术指导原则》[6]等一系列相关指导原则，用于规范和指导致癌试验研究。本文简要介绍动物致癌试验结果与人类相关性评估的必要性以及致癌试验与人类风险评估无关或可能无关的肿瘤等内容，为我国非临床药物致癌试验的结果分析和风险评估提出建议，并对我国药物非临床毒性病理学评价提供一定的参考。

1 动物致癌试验结果与人类相关性评估的必要性

ICH S1B《药物致癌试验指导原则》推荐致癌试验可采用1项大鼠2年长期试验和1项小鼠2年长期试验，或1项大鼠2年长期试验和1项转基因小鼠6个月试验[2]。ICH S1A《药物致癌试验必要性指导原则》[2]和中国于2010年颁布的《药物致癌试验必要性的技术指导原则》[6]（下称《指导原则》）均指出："啮齿动物致癌试验的结果与人类安全性评估的相关性经常引起争议，可能需要进行进一步的研究来探讨其作用方式，以帮助确定是否存在对人类的潜在致癌性。当啮齿动物致癌试验出现阳性结果时，可能需要进行进一步的研究探讨其作用机制，来评估与人类的相关性。"因此在啮齿动物致癌试验中分析肿瘤发生的作用方式（mode of action，MOA），评估其与人类的相关性，并进行风险评估，以对临床试验药物评价工作提供参考是有必要的。

2 致癌试验中与人类风险评估无关的肿瘤

2.1 大鼠胃酸分泌抑制引起的胃神经内分泌肿瘤（类癌）

大鼠胃神经内分泌细胞（肠嗜铬样细胞）的增生和肿瘤受胃泌素刺激影响较大。胃酸分泌抑制药物如质子泵抑制剂（如奥美拉唑）或组胺拮抗剂（如西米替丁）可引起胃酸生成减少，进而引起胃泌素增加[7-8]。引起胃萎缩的化学物质（如甲草胺和丁草胺）也可诱发此类肿瘤[9]。大鼠胃神经内分泌细胞密度较高而且对胃泌素增加非常敏感[10]，雌性大鼠比雄性大鼠更容易发生神经内分泌细胞肿瘤。人类仅在胃泌素水平超过400 pg·mL^{-1}时可见神经内分泌细胞的显著增生，这在临床治疗中是可控的。因此，药物致癌试验中大鼠出现此肿瘤并不意味着对人类的实际风险[11-13]。

2.2 大鼠α_{2u}-球蛋白肾病引起的肾肿瘤

雄性大鼠（特别是F344大鼠）的尿液中可检测到α_{2u}-球蛋白，该蛋白与透明小滴形成、近端小管上皮的非典型增生和肿瘤有关，但人类肾中没有此类蛋白[14]。其作用方式已经通过给予α_{2u}-球蛋白转基因小鼠*D*-柠檬烯试验予以证实[15]，因此，目前普遍认为，由α_{2u}-球蛋白蓄积引起的肾小管肿瘤不是人类风险识别的合适终点。与这种肿瘤效应相关的药物包括*D*-柠檬烯和三甲基戊烷[9,14,16]。同样，国际癌症研究机构（International Agency for Research on Cancer，IARC）的1个工作小组得出类似结论：仅通过α_{2u}-球蛋白肾病引起雄性大鼠肾肿瘤的药物并不对人类构成癌症危害[17]。

2.3 大鼠卵巢系膜平滑肌瘤

雌性大鼠长期暴露于β_2-肾上腺素受体刺激药物后，会引起卵巢系膜平滑肌肿瘤[11,18]。人类极少发生此类肿瘤，诱导大鼠产生此类肿瘤的药物（索特诺、美苏林、茨特罗、特布他林、瑞特罗和沙丁胺醇）与人类的癌症无关。

2.4 大鼠膀胱腔内环境改变引起的尿路上皮癌

大鼠模型多用于尿路上皮肿瘤的研究，在早期的研究中，人们认识到在膀胱腔内放置惰性颗粒物会引起尿路上皮肿瘤的增加[20]。大鼠膀胱尿路上皮缺乏紧密连接，浅层黏膜不能作为腔内屏障，使

底层组织容易受到慢性刺激[20-21]，因此大鼠对尿路上皮的损伤比小鼠更敏感。与其他种属相比，大鼠（尤其是雄性）膀胱腔内蛋白、硅酸盐沉淀、磷酸钙沉淀、结晶形成和尿结石更多[17,22-23]。啮齿动物的膀胱是水平的，不像人的垂直膀胱那样可以有效排空，因此，大鼠膀胱尿路上皮更容易产生慢性细胞损伤，导致细胞增生和肿瘤形成[20,24]，这种效应不会发生在人类身上[24-26]。IARC的1个工作小组已经得出结论，在尿液中含有磷酸钙沉淀物时，大鼠膀胱癌的产生并不能预测人类的癌症风险[17]。与这种肿瘤形成相关的条件和化学物质包括引起结晶尿的药物（PPARγ激动剂吡格列酮、PPARα/γ激动剂莫格他唑）和引起尿液pH值显著改变的药物（三聚氰胺、糖精、碳酸酐酶抑制剂和磷酸盐饮食）[17,19-25,27]。

2.5 大鼠阴道-宫颈颗粒细胞瘤

在雌性SD大鼠、Donryu大鼠和Wistar大鼠的阴道-宫颈区域，可见胞质呈嗜酸性的颗粒细胞增生性病变[28-29]，此类病变可能受雌激素影响。人类女性的外阴罕见颗粒细胞聚集，且没有证据表明其发病机制与大鼠颗粒细胞瘤相似。因此，这种病变被认为与人类无关。

2.6 啮齿动物肝过氧化物酶体增殖物激活受体α（PPARα）激动剂诱导的肝肿瘤

多种化学物质都能引起与过氧化物酶体增殖相关的啮齿动物肝肿瘤的增加[30]。与灵长类动物或人类相比，啮齿动物更容易受到过氧化物酶体增殖物激活受体α（peroxisome proliferator-activated receptor α，PPARα）激动剂诱导的肝过氧化物酶体增殖的影响[30-32]，其原因是因为PPARα在啮齿动物肝中具有更高表达[33]。据报道，在体外培养的大鼠肝细胞中，PPARα激动剂促进DNA合成并抑制细胞凋亡，但在人类肝细胞中，DNA合成受到抑制，而细胞凋亡增强[34]，这种差异可能与上述机制有关。啮齿动物PPARα激动剂的致癌性机制虽然尚未完全了解，但似乎与持续的肝细胞增殖有关[35-36]。IARC的1个工作小组建议，小鼠或大鼠的肝脏肿瘤如果仅继发于过氧化物酶体增殖[30]，则与人类癌症无关。

2.7 啮齿动物皮下注射或植入部位肉瘤

啮齿动物（特别是雄性）容易发生皮下肿瘤，无论是背景病变还是诱发性肿瘤[37]。这些肿瘤多被诊断为纤维组织细胞瘤、纤维肉瘤、脂肪肉瘤或平滑肌肉瘤，这些肿瘤可能是啮齿动物皮下植入固体材料后所产生的被称为奥本海默效应的固态效应所引起[38]。啮齿动物皮下注射非遗传毒性刺激物（如右旋糖酐铁）也可诱发上述肉瘤[37]。啮齿动物中引起此种作用的化学物质（包括重组人胰岛素[39]）均与人类癌症无关。

2.8 啮齿动物甲状腺-垂体反馈稳态被破坏引起的甲状腺肿瘤

甲状腺-垂体反馈稳态被破坏是啮齿动物（尤其是大鼠）甲状腺肿瘤发生的常见机制之一[11,43-44]。通过抑制碘化物的吸收（如高氯酸盐）、抗甲状腺药物（如丙基硫氧嘧啶）抑制激素合成、或与激素结合增强（如苯巴比妥）而使甲状腺激素清除增加，从而导致激素水平下降，进而反馈性引起促甲状腺激素水平增加，甲状腺滤泡细胞肥大、增生，最后形成肿瘤。不同物种对甲状腺激素稳态破坏的敏感性不同，大鼠最为敏感[45]。诱导大鼠肝-甲状腺激素结合增强的几种诱导剂（通常也与肝肿瘤的增加有关）对小鼠没有影响[46]。已知目前只有放射性物质暴露会导致人类甲状腺滤泡细胞肿瘤[17]。因此，目前认为啮齿动物中甲状腺作用的化学物质特异性数据可以用于风险评估[47]，通过适应性激素机制导致甲状腺肿瘤被认为与人类风险评估无关[11]。

3 致癌试验中与人类风险评估可能无关的肿瘤

3.1 小鼠卵巢管状腺瘤

这是一种良性肿瘤，主要发生在小鼠，含有管状、间质或混合性成分[48-49]。小鼠给予细胞毒性药物可发生管状间质腺瘤，但在其他实验动物和人类中未见报道，因此考虑可能与人类无关[48-50]。

3.2 小鼠膀胱间叶增生性病变

此类病变发生在膀胱后部靠近三角区的部位，也称为良性间叶性肿瘤[51-52]。小鼠给予与黄体酮和雌激素受体结合药物（如灌胃避孕药）可出现此类病变[53]。有足够的证据表明该病变是带有孕酮受体的间叶细胞的蜕膜反应[54-55]。人类未见此类病变，因此该病变对于人类的意义有待商榷。

3.3 大鼠腺垂体肿瘤

啮齿动物和人类发生的大多数垂体肿瘤是腺瘤[56-58]。这些常见的致死性肿瘤对雌性大鼠的影响比雄性大鼠更明显，且多发于老龄大鼠[59]。这些肿瘤中多数都含有催乳素细胞，表明其产生与老龄动物多巴胺含量减少有关[60]。使用镇静剂（多巴胺抑制剂）、长期给予雌激素和促性腺激素释放激素类药物（戈舍瑞林、亮丙瑞林和降钙素）、性腺切除术、甲状腺消融术、碘缺乏、给予致甲状腺肿大物质和

电离辐射都与垂体肿瘤增加有关[61]。综上所述，大鼠的垂体肿瘤是激素反馈干扰的结果，而在人类中则没有这种作用，女性高催乳素血症闭经经常与垂体肿瘤有关[62-63]。因此，在人类中，尽管长期服用避孕类固醇或雌激素替代治疗，但尚未确定与这些肿瘤的因果关系[62-63]。

3.4 大鼠甲状腺C细胞肿瘤

实验动物甲状腺C细胞的数量比人类多。甲状腺C细胞肿瘤既可以是背景病变，也可在啮齿动物癌症生物检测（rodent cancer bioassay，RCB）诱导发生，多见于大鼠（最常见）、小鼠和仓鼠[43,64-66]。增生性和肿瘤性甲状腺C细胞可以产生降钙素、神经紧张素和生长抑素[67-68]，大鼠还可见甲状腺C细胞增生[69-70]，Long-Evans大鼠品系还可发生C细胞髓样癌[65]。大鼠和人类的甲状腺C细胞增生都伴有血降钙素升高[43,64,66]。与对照组相比，给予诱发滤泡细胞肿瘤的放射性碘可减少C细胞肿瘤的数量[71]。雌性SD大鼠皮下注射给予艾塞那肽（抗糖尿病的非遗传毒性药物，剂量为人类暴露量的130倍）后可诱发产生良性C细胞腺瘤[72]。因此，由非遗传毒性化合物引起的C细胞增生和肿瘤似乎不会引起人类癌症风险。

3.5 大鼠阴蒂腺肿瘤

这种罕见的肿瘤散在发生，如果发生在受试物组大鼠，可能需要引起关注。目前没有化学物质被证明可重复诱导此类肿瘤发生，也没有发现潜在的机制。因此，该肿瘤的人类相关风险比较有限。

3.6 棕色脂肪组织肿瘤

棕色脂肪组织肿瘤常发生于大鼠纵隔或肾上腺周围区域，棕色脂肪组织目前被认为是一种内分泌器官[73-74]。据报道，噻唑烷二酮类抗高血糖药、咪唑并吡啶催眠药[39]、非选择性α-肾上腺素能受体拮抗剂酚妥拉明[73,75]，以及三唑酮类除草剂都会诱导产生此类肿瘤，但发病率较低，且多发于雄性大鼠。到目前为止，还没有确切的化学物质被证明能诱发棕色脂肪组织瘤前病变或早期肿瘤。研究表明，噻唑烷二酮类在大鼠和小鼠中均可诱导剂量相关性棕色脂肪组织增生，但在持续暴露2年后，此类增生并未进展为瘤前病变或肿瘤[76]。在1项以观察棕色脂肪组织结构、功能和病理研究中，年轻（6周龄）和成年（36周龄）大鼠暴露于酚妥拉明12个月后，并未发现棕色脂肪组织增生增多、凋亡减少或瘤前病变[73]，且经过4周恢复期可恢复。棕色脂肪组织肿瘤在啮齿动物和人类中都是非常罕见的良性肿瘤[73]。迄今为止，恶性棕色脂肪组织瘤尚未在人类中得到明确的描述[77-79]。对啮齿动物噻唑烷二酮类诱导的棕色脂肪组织肿瘤综述[76]进一步证明其为良性肿瘤，而且由于啮齿动物与人类的糖异生、蛋白质分解代谢、中间代谢和能量（体温）稳态及反馈回路都不相同，因此其与人类相关风险有限。

3.7 大鼠乳腺纤维腺瘤

大鼠纤维腺瘤是一种良性肿瘤，具有少量腺上皮成分，周围结缔组织增生明显。与人类女性常见的管内型纤维腺瘤[80-81]几乎没有相似之处，后者是激素反应性的[82]。纤维腺瘤是所有常规使用的大鼠品系中最常见的乳腺背景肿瘤，通常发生于50周龄以上，不会进展为恶性肿瘤。因此，将纤维腺瘤和癌进行合并分析是不合适的。纤维腺瘤本身与人类的相关风险有限。大鼠纤维腺瘤主要受催乳素刺激引起[83-85]，而人类的纤维腺瘤主要受雌激素（主要）和孕酮刺激引起[83-84,86]。

3.8 大鼠单核细胞白血病

大鼠单核细胞白血病是致死性肿瘤，也被称为大颗粒淋巴细胞白血病（large granular lymphocyte leukemia，LGL），最初发生于脾脏，然后见于肝、肺、淋巴结和骨髓。在F344大鼠中，18月龄以上动物发病率较高（雄性发病率62%、雌性42%）[87]。没有任何化学物质被证明可重复诱导产生这种肿瘤，因此其发病机制尚未明确。据报道，许多化学物质（呋喃、碘化甘油、邻苯二甲酸二异壬酯和二甲基吗啉代氨基磷酸酯等）与大鼠单核细胞白血病的发生率增加可能有关[88-89]，但该肿瘤与人类癌症风险可能无关。

3.9 大鼠胰岛细胞肿瘤

所有种属老龄啮齿动物（特别是大鼠）都会发生背景性胰岛细胞肿瘤，包括胰岛素性（为主）、胰高血糖素性、生长抑素性和多肽阳性细胞性等多种类型[90-93]。在人类中此类肿瘤很少见（约占所有胰腺肿瘤的1%）[94]。由于胰腺内分泌部和外分泌部稳态的差异，全身性抗糖异生引起的持续低血糖不会引发啮齿动物摄食量的增加，从而导致了能量稳态和代谢的长期紊乱[95-96]。试验结果表明，无论添加烟酰胺或吡啶酰胺与否[97]，链脲霉素或四氧嘧啶都可诱导大鼠产生胰岛细胞肿瘤，尽管其作用方式尚未彻底阐明，但很可能是基于特定种属的激素反馈性干扰引起，而这种作用方式与人类无关。

3.10 大鼠阴囊鞘膜间皮瘤

起源于睾丸和阴囊鞘膜的浆膜，属于间叶组织

的病变，包括增生和肿瘤[98]，F344大鼠较常见（约3%）[87]。阴囊的病变常与睾丸肿瘤的发生有关，特别是常见的睾丸间质细胞肿瘤[99]，其发病机制之一可能为物理刺激。因此，仅诱导此种肿瘤产生的化学物质可能与人类无关。肿瘤中分泌增多的化学物质（如丙烯酰胺、溴酸钾和五氯苯酚）具有多元化结构，其作用方式尚未阐明。但是，上述发病机制和特点均与人类间皮瘤或其他癌症无关[100]。

3.11 大鼠皮肤纤维瘤

这种皮下组织良性肿瘤，通常为局限性背景肿瘤，与腺体成分萎缩的乳腺纤维腺瘤很难区分，多发生在50周龄以上的各品系大鼠，雄性较雌性多发。如果该病变出现一些恶性特征，则需要特别关注，最近研究表明，PPARα和（或）γ激动剂可以增加纤维肉瘤的发生率。然而，大鼠皮肤纤维瘤与人类的相关性尚不明确[101]。

3.12 大鼠脾肉瘤

F344大鼠长期给予苯胺（及苯胺基化合物）、对-氯苯胺、邻-甲苯胺可观察到脾肉瘤[102-103]。推测其可能的作用方式如下：苯胺导致高铁血红蛋白血症，脾窦内红细胞聚集、铁蓄积并引起氧化应激，继而导致白细胞介素1α、白细胞介素1β和肿瘤坏死因子-α（tumor necrosis factor-α，TNF-α）增加，进而导致纤维化增多和肿瘤形成[104-105]。雄性大鼠给予抗疟疾药（同时给予乙胺嘧啶）和抗麻风病药物氨苯砜（4，4′-二氨基-二苯砜-苯基砜）时，可出现脾充血、坏死和肉瘤[102-103]。然而，人类患者使用上述药物治疗多年并未引起脾肉瘤，因此这种肿瘤可能与人类无关。

3.13 啮齿动物肾上腺髓质嗜铬细胞瘤

啮齿动物中最常见的肾上腺髓质肿瘤是嗜铬细胞瘤，最常见于仓鼠，其次为大鼠和小鼠[57,87]。在许多情况下，嗜铬细胞瘤与全身性低氧血症有关，这会刺激肾上腺髓质分泌儿茶酚胺，慢性内分泌功能亢进可能导致代偿性肾上腺髓质增生和肿瘤形成，而且大鼠嗜铬细胞瘤通常伴有弥漫性肾上腺髓质增生[57]。引起此种反馈干扰的物质包括乳糖、糖醇和Ca^{2+}[106-107]。通过此种途径诱发的嗜铬细胞瘤很可能与人类无关[108]。

3.14 啮齿动物子宫内膜肿瘤

大鼠给予非甾体抗雄激素比卡鲁胺会引起子宫内膜癌的产生[109]，该药物仅用于男性前列腺癌的治疗，因此在雌性大鼠中发现的肿瘤被认为与人类无关。此外，长期暴露于多巴胺受体激动剂培高利特会导致大鼠子宫内膜肿瘤和小鼠平滑肌瘤或肉瘤。目前认为这两种肿瘤都反映了催乳素的抑制和雌激素或催乳素反馈稳态的破坏[11,39]，而这种机制与人类无关。

3.15 啮齿动物前胃鳞状细胞癌

啮齿动物前胃是胃的一部分，位于食道和腺胃之间，衬覆鳞状上皮，人类不存在该结构。除B6C3F1小鼠外，前胃鳞状细胞癌在其他种属都比较罕见。许多DNA反应性物质通过经口灌胃给药直接接触前胃，可在啮齿动物中诱导此类肿瘤[110]。多数情况下，非遗传毒性药物（如丁基羟基苯甲醚）会增加这种肿瘤的发生率。表观遗传机制似乎涉及导致促长作用的慢性刺激，需要大剂量暴露[13,26,111]。IARC的1个工作小组认为长期接触后仅产生前胃肿瘤的表观遗传致癌物可能与人类的相关性较小[13]，因为人类接触需要超过时间和剂量阈值才能引起致癌性反应。事实上，上述化学物质中没有一种与人类癌症有关。

3.16 啮齿动物哈氏腺肿瘤

这种局质分泌眼附属腺的自发性肿瘤多见于小鼠（最常见，发生率为0.5%～15%）、仓鼠和大鼠[57,87,112]。许多遗传毒性药物（如静脉注射更昔洛韦）[73]和非遗传毒性药物（如唑来膦酸）[39]可诱发小鼠哈氏腺腺癌。由于人类不存在该腺体，所以此类肿瘤可能与人类无关。

3.17 啮齿动物血管瘤或血管肉瘤

血管瘤/血管肉瘤属于小鼠常见的背景病变，大鼠中较少发生，人类则很少发生。此类肿瘤在CD-1小鼠中多呈多灶性发生，雌、雄动物发生率分别为7%～32%和6%～33%，通常受累及的器官（＞2%）包括雄性动物的脾、肝、淋巴结、睾丸、皮肤和胰腺，以及雌性动物的子宫、脾、肝、卵巢、淋巴结和心[113]。在给予具有DNA反应性的化学物质（如氯乙烯、溴化乙烯和钍造影剂）和表观遗传性化学物质（如普瑞巴林、埃尔米隆PPARα和（或）γ激动剂，2-丁氧乙醇）的啮齿动物中可见血管瘤和血管肉瘤发生率的增加[114-119]。啮齿动物血管肉瘤的表观遗传诱导中存在的常见作用方式包括组织缺氧、溶血、呼吸减少和脂肪细胞生长等关键引发因素，所有这些都可导致血管生成和（或）红细胞生成异常[114-115,118]。人类未见类似的物种特异性多灶性病变的报道，也没有相关诱导剂引起此类肿瘤[115,120-121]。

3.18 啮齿动物组织细胞肉瘤

组织细胞肿瘤多在老龄化小鼠中发现，在老龄

化大鼠中不常见，主要累及肝和子宫[121]。目前未见化学物质可以增加此种肿瘤的发生率，因此其可能与人类无关[122]。

3.19 苯巴比妥样酶诱导剂诱导的啮齿动物肝肿瘤

以苯巴比妥为原型化合物的多种化合物通过一种涉及肝增生的作用方式引起小鼠和大鼠肝肿瘤的增加[123-124]。根据药动学和药效学因素的分析，认为此类作用方式在人类中不太可能出现[124-125]。流行病学调查数据也显示人类发生此类癌症的风险并未增加[126]。

3.20 啮齿动物骨瘤或骨肉瘤

原发性骨肿瘤在啮齿动物和人类都不常见，啮齿动物背景骨肿瘤同样比较罕见[127-128]。电离辐射、氯乙烯和亚硝胺类物质都可诱发啮齿动物发生骨肿瘤[129-130]，小鼠长期给予己烯雌酚或17β-雌二醇也会产生骨肿瘤[131]。此外，大鼠给予抗骨质疏松药物重组甲状旁腺激素会产生剂量相关的骨质增生、骨肉瘤、骨瘤和成骨细胞瘤[39-42]。大鼠连续给予糖皮质激素2年也会出现骨质增生和骨肿瘤[132]。小鼠给予雌激素前体和前列腺素E样化合物也会导致骨质增生和骨肉瘤[133-134]。所有上述情况的最初作用方式似乎是对骨骼生长模式的内分泌反馈稳态的持续（长期）干扰，与人类无关。

3.21 啮齿动物激素稳态破坏引起的睾丸间质细胞肿瘤

睾丸间质细胞肿瘤在老龄F344大鼠中发生率很高（＞80%）[87]，且均为良性肿瘤。大鼠中黄体生成素升高[135]、小鼠中黄体生成素升高[136]或给予雌激素激动剂（如己烯雌酚或他莫西芬）[137-138]都可以引起上述病变。人类睾丸间质细胞肿瘤罕见，而且能够引起大鼠睾丸肿瘤增多的化合物（乳糖、糖醇、西咪替丁、肼嗪、吉非罗齐、卡马西平、阿糖腺苷、伊拉地平、外源性促性腺激素、黄体生成素释放激素类似物、氟他胺、麦角碱、非那雄胺等）并不诱导人类发生此种或其他类型睾丸间质细胞肿瘤。因此，现有信息表明：在啮齿动物中诱导睾丸间质细胞肿瘤的非遗传毒性化合物与人类无关[139]。

4 结语

所有非临床药物评价研究都是为临床研究和临床应用提供参考，以实现非临床到临床的转化，对于啮齿动物致癌试验中的阳性试验结果，最值得关注的就是其与人类的相关性[140]。对于啮齿动物致癌试验中发生的肿瘤，评估其潜在的与人类癌症的相关性经过了一系列观念上的改变。以前，所有啮齿动物的致癌物均被认为是潜在的人类癌症风险物，这一概念体现在1958年美国联邦食品、药品和化妆品法案（Federal Food，Drug，and Cosmetic Act，FFDCA）的德莱尼条款中，该条款规定无论浓度如何，任何被确定对动物具有致癌性的化学物质都不被允许作为食品添加剂。随后，对致癌作用机制的深入理解促进了风险评估的改进[141]，1992年以后，国际癌症研究机构接受了评估化学物质与人类致癌风险评估有关的机制数据[142]。

目前，在评估潜在的人类癌症风险时，监管机构往往会从作用机制方面来进行判断，如果被检测的化学物质具有明显DNA反应性（遗传毒性致癌物质），此类化学物质往往具有多组织靶点、潜伏期短、多种属和性别肿瘤阳性等特点，那么肿瘤的增加强烈暗示对人类的潜在风险[142-146]，对人类危害的假设是有充分根据的。如果被检测的化学物质属于表观遗传性致癌物，不直接产生DNA损伤，其致癌作用机制具有典型的物种、性别和组织特异性，可能只在特定的啮齿动物中（如雄性大鼠的α_{2u}-球蛋白肾病诱导剂）或仅在高毒性剂量下（如氮三乙酸肾病）发挥潜在的致癌作用。这些影响要么被认为与人类风险无关[14]，要么可以进行暴露阈值的风险评估[147]来判断对人类的危害性。因此，致癌试验中对出现阳性结果的肿瘤进行作用方式的探讨，并分析这种作用方式与人类风险评估是否相关，对于啮齿动物致癌试验的结果分析和风险评估是非常有必要和有意义的。由此可见，药物非临床是否致癌的毒性病理学评价结果，对于药物能否进入临床开发有重要的参考价值。

利益冲突 所有作者均声明不存在利益冲突

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