Invited Review

Pathogenesis of chemically induced nasal cavity tumors in rodents: contribution to adverse outcome pathway

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Abstract: The pathogenesis of nasal cavity tumors induced in rodents has been critically reviewed. Chemical substances that induce nasal cavity tumors in rats, mice, and hamsters were searched in the National Toxicology Program (NTP), International Agency for Research on Cancer (IARC), and Japan Bioassay Research Center (JBRC) databases, in addition to PubMed. Detailed data such as animal species, administration routes, and histopathological types were extracted for induced nasal cavity tumors. Data on non-neoplastic lesions were also extracted. The relationship between the tumor type and non-neoplastic lesions at equivalent sites was analyzed to evaluate tumor pathogenesis. Genotoxicity data were also analyzed. Squamous cell carcinoma was the most frequent lesion, regardless of the dosing route, and its precursor lesions were squamous metaplasia and/or respiratory epithelial hyperplasia, similar to squamous cell papilloma. The precursor lesions of adenocarcinoma, the second most frequent tumor type, were mainly olfactory epithelial hyperplasia, whereas those of adenoma were respiratory epithelial lesions. These pathways were consistent among species. Our results suggest that the responsible lesions may be commonly linked with chemically-induced cytotoxicity in each tumor type, irrespective of genotoxicity, and that the pathways may largely overlap between genotoxic and non-genotoxic carcinogens. These findings may support the documentation of adverse outcome pathways (AOPs), such as cytotoxicity, leading to nasal cavity tumors and the integrated approaches to testing and assessment (IATA) for non-genotoxic carcinogens. (DOI: 10.1293/tox.2023-0098; J Toxicol Pathol 2024; 37: 11–27)

Key words: nasal cavity, tumorigenicity, rodent, pathogenesis

Introduction

The Organisation for Economic Co-operation and Development (OECD) has driven the development of adverse outcome pathways (AOPs) as promising tools for regulatory acceptance[1]. Recently, the OECD has been actively promoting AOPs for systemic toxicity, including carcinogenicity. The framework of AOPs is expected to provide critical information on the causal links between a molecular initiating event, intermediate key events at the cellular, tissue, and organ levels, and adverse outcomes at the individual or population level[2]. AOPs may offer a biological context for regulatory decision making to facilitate the development of integrated approaches for testing and assessment (IATAs)[3–5]. However, the established IATAs are currently limited to skin sensitization, skin irritation, and eye irritation.

Non-genotoxic carcinogens are the targets of ongoing OECD projects for IATAs[6]. In terms of regulatory control, carcinogens are largely divided into two categories: genotoxic and non-genotoxic. Genotoxic carcinogens are readily screened using genotoxicity assays. Therefore, an IATA for non-genotoxic carcinogens is critical for assessing the risks associated with carcinogens that cannot be clarified using genotoxicity assays. Such chemicals can cause cytotoxicity, which is a major non-genotoxic mechanism without strong *in vivo* genotoxicity, as exemplified by formaldehyde[7].

In this report, the pathogenesis of chemically induced nasal cavity tumors in rodents is critically reviewed. The findings of this report support the documentation of AOPs leading to nasal cavity tumors and contribute to the documentation of IATAs for non-genotoxic carcinogens in cur-

rent OECD projects.

Methods

Search for chemical substances inducing nasal cavity tumors

Nasal cavity tumors rarely occur spontaneously in rodents[8], and therefore, this provides a useful model to understand the effect of chemical substances on tumorigenesis. The databases of the International Agency for Research on Cancer (IARC), Japan Bioassay Research Center (JBRC), and National Toxicology Program (NTP), as well as in PubMed, were searched for reports of chemical substances inducing nasal cavity tumors in animal studies using rats, mice, and hamsters. The exposure routes were divided into inhalation and non-inhalation routes, including oral administration, subcutaneous injection, and intraperitoneal injection. Potential exposure-unrelated or histopathologically unspecified tumors were excluded from the analysis of tumor pathogenesis.

Standardization of nasal cavity tumor terminology

For rodent studies in which nasal cavity tumors were induced by chemical substances, information on animal species, administration route, histological tumor type, and possible coexisting non-neoplastic lesions was extracted from the relevant databases or literature.

Information on the histological types of nasal cavity tumors was initially extracted using terms cited in pertinent data sources and then standardized based on more recent tumor terminology, particularly for those found in the International Harmonization of Nomenclature and Diagnostic Criteria for Lesions in Rats and Mice (INHAND)[9]. However, specific tumors arising from olfactory epithelial cells, for which many synonymous terms exist, were unified as neuroepithelial carcinoma, a standardized term in the IN-HAND. To standardize the terms listed in INHAND, histological descriptions and photomicrographs of the neoplastic lesions were referenced using relevant data sources.

Information on the original tissues from which the tumors developed was extracted from the relevant data sources. Tissues of origin were broadly categorized as squamous epithelium (SE), respiratory epithelium (RE), or olfactory epithelium (OE) based on descriptions in the relevant data sources. More specific terms, such as transitional epithelium (TE), submucosal gland (SG), nasal gland (NG), and Bowman's gland (BG), were also extracted. Then, the narrow band of TE between the SE and RE was classified as RE[10] and SG and NG were unified as SG at the final step (Fig. 1).

Analysis of the pathogenesis of nasal cavity tumors

For each histological type of nasal cavity tumor, the chemical substances responsible were listed according to the rodent species and route of administration. Histopathological findings of non-neoplastic lesions, including degenerative and/or regenerative changes in the nasal cavity, were extracted from data sources that reported the induc-

tion of nasal cavity tumors. The relationship between the nasal cavity tumors and non-neoplastic lesions induced at the corresponding sites was analyzed histopathologically. The reliability of the data sources was critically assessed with special attention to the experimental design. Although histological types of nasal cavity tumors were classified in accordance with the standardized nomenclature for nasal cavity tumors in INHAND, for mesenchymal tumors, such as rhabdomyoma, rhabdomyosarcoma, hemangioma, hemangiosarcoma, and fibrosarcoma, the terms in the data sources were used as they were consistent with the terms for the cardiovascular system and soft tissues in INHAND[11, 12].

Histopathological findings of non-neoplastic lesions in the nasal cavity were also extracted from short-term animal studies on relevant chemical substances using PubMed. For the NTP and JBRC studies, histopathological findings of non-neoplastic lesions were also extracted from preliminary dose-setting studies, if available.

Non-neoplastic lesions, such as REs and OEs, were classified based on the affected tissue. To analyze the relationship between neoplastic and non-neoplastic lesions, associated lesions were identified from the histopathological findings of non-neoplastic lesions in the same tissue as the neoplastic lesion. The robustness of the information on the relationship between neoplastic and non-neoplastic lesions was evaluated according to the degree of coexisting association of both lesions. For chemical substances described in multiple data sources, the information was analyzed for each data source, and the results were analyzed in an integrated manner after the reliability of the information was assessed. Genotoxicity information was mainly collected from the European Union Reference Laboratory for Alternatives to Animal Testing (ECVAM)[13]. Information was retrieved from the NTP reports and other literature on chemical substances not included in the ECVAM database.

Results

Overview of nasal cavity tumors induced in rodents

As shown in Supplementary Tables 1 and 2[14–120], 72 chemical substances that induce nasal cavity tumors in rodents were extracted. Nasal cavity tumors were induced in rodent studies following exposure to 40 substances by inhalation, 38 substances by non-inhalation, and 6 substances by both routes. As summarized in Tables 1, 2 and 3, in the rat inhalation studies, the following tumors were detected in decreasing order of incidence: squamous cell carcinoma, adenoma, adenocarcinoma, neuroepithelial carcinoma, squamous cell papilloma, adenosquamous carcinoma, and mesenchymal tumors. In contrast, in rat non-inhalation studies, the order of decreasing incidence was as follows: squamous cell carcinoma, adenocarcinoma, squamous cell papilloma, adenoma, neuroepithelial carcinoma, mesenchymal tumor, and adenosquamous carcinoma. In mouse inhalation studies, the following tumors were detected, in order of decreasing incidence: mesenchymal tumors, adenomas, squamous cell carcinomas, adenocarcinomas, and squamous cell pap-

illomas. In a mouse non-inhalation study, squamous cell carcinoma, adenocarcinoma, and adenoma were reported in one study. In hamster inhalation studies, squamous cell carcinoma, adenoma, and neuroepithelial carcinoma were each reported in one study, whereas in hamster non-inhalation studies, the following tumors were detected in order of decreased incidence: adenoma, squamous cell papilloma, adenocarcinoma, neuroepithelial carcinoma, and squamous cell carcinoma.

Estimated pathogenesis for nasal cavity tumors

When analyzing the relationship between induced neoplastic lesions and associated histopathological non-neoplastic lesions in the nasal cavity, only data with strong reliability were used to estimate the pathogenesis of neoplastic lesions. Thus, studies that did not specify the histological types of tumors nor cited associated non-neoplastic lesions were excluded (Tables 1 and 2). Since sex differences were not substantially evident in the induction of nasal cavity tumors throughout the studies analyzed, sex was not specifically reported.

Squamous cell papilloma

As shown in Supplementary Table 1[14–82], squamous cell papilloma was induced by 10 substances, including butyl 2,3-epoxypropyl ether, 1,2-dibromo-3-chloropropane, 1,2-dichloropropane, 1,2,3,4-diepoxybutane, epichlorohydrin, 2,3-epoxypropyl methacrylate, formaldehyde, hexamethylphosphoramide, hydrazine, and vinyl acetate, in rat inhalation studies. As shown in Tables 1 and 4, squamous cell papillomas appeared to develop from the RE or TE in most cases. The pathogenesis of these ten substances was analyzed in association with non-neoplastic or preneoplastic lesions (Tables 1 and 3). Consequently, degenerative changes in the RE and squamous metaplasia are commonly observed in the confirmed cases. Additionally, regeneration was observed for hexamethylphosphoramide[57], and hyperplasia of the RE or TE was observed for 1,2-dichloropropane[37]. Thus, a plausible pathway leading to squamous cell papilloma involves cell injury and subsequent regenerative hyperplasia of the RE or TE, followed by squamous metaplasia and hyperplasia (Fig. 1).

In non-inhalation studies in rats, eight substances induced squamous cell papilloma, including diallylnitrosamine, dimethylvinyl chloride, 1,4-dinitrosopiperazine, N-nitrosomethyl-n-octylamine, N-nitrosomethyl-n-pentylamine, N-nitrosomethyl-n-propylamine, NNK, and NNN (Supplementary Table 2[83–120]). As shown in Tables 2 and 4, similar to the rat inhalation studies, squamous cell papilloma consistently developed from RE in confirmed cases. The roles of dimethylvinyl chloride and 1,4-dinitrosopiperazine in the pathogenesis of squamous cell papilloma were evaluated (Tables 2 and 3). The pathway leading to squamous cell papilloma in non-inhalation rat studies has also been suggested to involve squamous hyperplasia and/or metaplasia of the RE (Fig. 1).

In mouse inhalation studies, squamous cell papillomas

were induced by 1,2-dibromo-3-chloropropane, 1,2-dibromoethane, glycidol, and propylene oxide (Supplementary Table 1). As shown in Tables 1 and 4, similar to rat studies, squamous cell papilloma appeared to develop from the RE in three cases, excluding propylene oxide. These three substances were subjected to pathogenic analysis for squamous cell papillomas (Tables 1 and 3). This pathway may be involved in the development from squamous hyperplasia, metaplasia, and/or dysplasia to squamous cell papilloma (Fig. 1). Squamous cell papilloma was not induced in the mouse non-inhalation studies.

In hamster non-inhalation studies, N-nitroso-2,6-dimethylmorpholine, N-nitrosohexamethyleneimine, nitrosomorpholine, NNK, and NNN induced squamous cell papilloma (Supplementary Table 2). As shown in Tables 2 and 4, similar to rat or mouse studies, squamous cell papilloma appeared to develop from the RE in confirmed cases. Among these five substances, only N-nitroso-2,6-dimethylmorpholine (orally administered or subcutaneously injected) was evaluated for the pathogenesis of squamous cell papilloma (Tables 2 and 3). This pathway may proceed in the order of squamous hyperplasia, metaplasia, and dysplasia, leading to squamous cell papilloma via both exposure routes (Fig. 1). Squamous cell papillomas have not been reported to be induced in hamster inhalation studies.

Squamous cell carcinoma

The following 23 substances have been shown to induce squamous cell carcinoma in rat inhalation studies (Supplementary Table 1): acetaldehyde, acrolein, allyl glycidyl ether, bis(chloromethyl)ether, butyl 2,3-epoxypropyl ether, 1,2-dibromo-3-chloropropane, 1,2-dibromoethane, 1,2,3,4-diepoxybutane, dimethyl sulfate, 1,4-dioxane, epichlorohydrin, 2,3-epoxypropyl methacrylate, formaldehyde, furfuryl alcohol, glycidol, hexamethylphosphoramide, hydrazine, methyl acrylate, methyl methanesulfonate, N-nitrosodimethylamine, N-nitrosomethylvinylamine, phenylglycidyl ether, and vinyl acetate. Similar to squamous cell papilloma, squamous cell carcinoma develops from the RE or TE in most cases (Tables 1 and 4). Moreover, for hexamethylphosphoramide and phenylglycidyl ether, squamous cell carcinoma appeared to develop from the SG or NG in the RE[57, 58, 72]. For acetaldehyde, 1,2-dibromo-3-chloropropane, and vinyl acetate, squamous cell carcinoma also appeared to develop from the OE and RE[14, 32, 79, 121, 122].

Eighteen substances, excluding bis(chloromethyl)-ether, dimethyl sulfate, methyl methanesulphonate, N-nitrosodimethylamine, and N-nitrosomethylvinylamine, were subjected to pathogenesis analyses (Tables 1 and 3). The terms atypical squamous hyperplasia and squamous hyperplasia with atypia used in the literature were standardized as dysplasia[9]. Squamous cell metaplasia derived from degenerative changes in the RE was noted in most cases (Table 1). Additionally, regeneration was noted for formaldehyde, hexamethylphosphoramide, phenyl glycidyl ether, and vinyl acetate[57, 72, 79, 123–125]. Squamous hyperplasia was observed for acetaldehyde, 1,4-dioxane, and

Table 1. Nasal Cavity Tumors and Associated Non-neoplastic Lesions Based on Inhalation Exposure, and Related Genotoxicity Data of Each Substance

Chemical substances	Species	Nasal cavity tumors[a] (sites[b])	Associated non-neoplstic lesions[c] (sites[b])	Genotoxicity[d]
acetaldehyde	rat	SCC (RE/OE); ADC (OE)	MET (RE); DEG, HYP, MET (OE)	A(-), IV(+)
acrolein	rat	SCC; RM	HYP, MET(RE); ATR, MET(OE); MET(NG/BG)	A(+/-), IV(+)
	mouse	AD	HYP, MET(RE); ATR, MET(OE); MET (NG/BG)	
allyl glycidyl ether	rat	AD (RE); NEC (OE); SCC (RE)	HYP, MET (RE); DEG, MET (OE)	A(+), IV(+)
	mouse	AD (RE); HA	DEG, HYP, MET, DYS (RE); MET (OE)	
butyl 2,3-epoxypropyl ether	rat	PAP; SCC; NEC; AS	HYP, MET(RE); ATR, MET(OE); HYP(SG)	A(+), IV(+)
	mouse	HA; SCC	HYP(RE/TE); MET(OE); MET(SG)	
crotonaldehyde	rat	AD; RS	HYP, MET (RE); ATR, MET (OE)	A(+), IV(+)
cumene	rat	AD (RE)	HYP (RE); DYS (OE)	A(-), IV(+)
1,2-dibromo-3-chloropropane	rat	AD (RE); ADC (OE); PAP (RE); SCC (RE/OE)	ATR (OE); HYP, MET, DYS (RE)	A(+), IV(+)
	mouse	PAP (RE); SCC, AD (RE); ADC, HS, FS (OE)	ATR (OE); HYP, MET (RE)	
1,2-dibromoethane	rat	AD; ADC; SCC; CA/NOS	HYP, MET (RE)	A(+), IV(+)
	mouse	PAP (RE); AD (RE); SCC (OE); ADC (OE); HS	HYP (RE)	
1,4-dichloro-2-butene	rat	AD (RE); ADC (OE); AS (OE); RS (OE)	ATR, HYP, MET, DYS (OE)	A(+), IV(+)
1,2-dichloropropane	rat	PAP (RE/TE); NEC (OE)	HYP, MET (RE/TE); ATR (OE)	A(+), IV(-)
1,2,3,4-diepoxybutane	rat	PAP (RE); SCC (RE); ADC	DEG, ATR, MET	A(+), IV(+)
1,4-dioxane	rat	SCC (RE); RS; NEC	MET (RE); ATR, MET (OE)	A(-), IV(+/-)
epichlorohydrin	rat	PAP (RE); SCC (RE)	HYP, MET (RE)	A(+), IV(+)
1,2-epoxybutane	rat	AD (RE)	HYP, MET (RE); ATR (OE)	A(+), IV(+)
2,3-epoxypropyl methacrylate	rat	AD; ADC; AS; PAP; SCC; NEC; HS	HYP, MET, DYS (RE/TE)	A(+), IV(+)
	mouse	AD; ADC; HS; HA	HYP (RE); DEG, MET (RE); NEC, MET (OE); MET (NG/BG)	
formaldehyde	rat	PAP (RE); SCC (RE); AD (RE/TE)	HYP, MET, DYS (RE)	A(+), IV(+/-)
	mouse	SCC	MET, DYS (RE)	
furfuryl alcohol	rat	AD (RE); SCC (RE); CA NOS	DEG, HYP, MET (RE); ATR, DEG, HYP, MET (OE)	A(-), IV(-)
glycidol	rat	SCC (RE/TE); AD (RE/TE); ADC (RE/TE)	HYP, MET, DYS (RE); ATR (OE); DYS (NG)	A(+), IV(+)
	mouse	HA; HS; AD/ADC (RE/NG); PAP, SCC (RE)	HYP, MET, DYS (RE); MET (OE, SG); HYP (TE)	
hexamethylphosphoramide	rat	PAP (RE); SCC (RE/TE/SG); AD (RE); ADC (RE); AS (RE)	DEG, MET (RE); MET (NG)	A(+/-), IV(+)
hydrazine	rat	PAP; SCC; AD (RE/TE); ADC	DEG (RE/TE/OE); HYP, MET (TE)	A(+), IV(+)
	hamster	AD (RE/TE)	DEG, HYP (RE/TE)	
methyl acrylate	rat	SCC (RE)	HYP, MET (RE); ATR, HYP, MET (OE); DEG (NG/BG)	A(-), IV(+/-)
naphthalene	rat	AD (RE); NEC (OE)	ATR, HYP (OE); HYP, MET (RE); HYP, MET (BG)	A(-), IV(+/-)
phenylglycidyl ether	rat	SCC (RE/NG)	MET, DYS (RE, NG)	A(+), IV(-)
propargyl alcohol	rat	AD (RE/TE)	HYP (RE/NG/BG); ATR, DEG, MET, HYP (OE)	A(+), IV(+)
	mouse	AD (RE/TE)	HYP (RE/TE/NG/BG) MET (RE); ATR, MET (OE)	
propylene oxide	rat	AD (RE/NG)	HYP, MET (RE)	A(+), IV(+)
vinyl acetate	rat	PAP, SCC (RE/TE/OE)	ATR, HYP, MET (OE)	A(-), IV(+)
vinyl chloride	rat	ADC (OE/BG); NEC	DYS (OE/BG)	A(+), IV(+)
N-vinyl-2-pyrrolidone	rat	AD (RE/SG); ADC (OE/BG)	ATR (OE); HYP (RE/OE/SG); MET (OE)	A(-), IV(-)

[a] Abbreviated tumor types are as follows: AD: adenoma; ADC: adenocarcinoma; AS: adenosquamous carcinoma; CA/NOS: carcinoma not otherwise specified; FS: fibrosarcoma; HA: hemangioma; HS: hemangiosarcoma; ME: mucoepidermoid tumor; NEC: neuroepithelial carcinoma; PAP: squamous cell papilloma; RM: rhabdomyoma; RS: rhabdomyosarcoma; SCC: squamous cell carcinoma.

[b] Abbreviated nasal sites are as follows: BG: Bowman's gland; NG: nasal gland; OE: olfactory epithelium; RE: respiratory epithelium; SG: submucosal gland; TE: transitional epithelium.

[c] Abbreviated lesions are as follows: ATR: atrophy; DEG: degeneration; DYS: dysplasia; HYP: hyperplasia; MET: metaplasia; NEC: necrosis.

[d] Abbreviations are as follows: A: Ames test; IV: *in vivo* tests.

Table 2. Nasal Cavity Tumors and Associated Non-neoplastic Lesions Based on Non-inhalation Exposure, and Related Genotoxicity Data of Each Substance

Chemical substances	Species	Exposure[a]	Nasal cavity tumors[b] (sites[c])	Associated non-neoplastic lesions[d] (sites[c])	Genotoxicity[e]
p-cresidine	rat	oral	AD (RE); ADC (RE/OE); SCC; NEC	HYP, MET (RE/NG)	A(+), IV(+)
2,3-dibromo-1-propanol	rat	dermal	AD (RE); ADC (RE)	DYS (RE/OE)	A(+), IV(-)
N,N-dimethyl-p-toluidine	rat	oral	AD (RE/TE); ADC (RE/TE)	HYP (TE/RE); HYP, MET (OE/NG/BG); DEG (OE/BG)	A(-), IV(+)
dimethylvinyl chloride	rat	oral	PAP, SCC (RE/SG); ADC (RE/SG); RS, CA/NOS	HYP, MET	A(+), IV(+)
1,4-dinitrosopiperazine	rat	oral	ADC (OE); AS (OE); PAP (RE)	HYP (RE/OE)	A(+)
1,4-dioxane	rat	oral	SCC (RE); ADC, NEC (OE); RS (OE)	HYP, MET (RE); ATR, MET (OE)	A(-), IV(+/-)
N-nitrosodiethylamine	hamster	oral	UDC (OE)	DYS (OE)	A(+), IV(+)
	hamster	*it* injection	UDC (OE)	DYS (OE)	
N-nitroso-2,6-dimethylmorpholine	hamster	oral	PAP (RE); ADC (OE)	HYP, META, DYS (RE)	A(+)
	hamster	*sc* injection	PAP (RE); ADC	HYP, META, DYS (RE)	
1-nitroso-4-methylpiperazine	rat	oral	ADC (OE)	DEG, HYP (OE)	A (+)
2,6-xylidine	rat	oral	AD (RE); ADC (BG); CA/NOS; RS	HYP, MET	A(+), IV(-)

[a] abbreviated routes are as follows: *it*: intratracheal; sc: subcutaneous.
[b] Abbreviated tumor types are as follows: AD: adenoma; ADC: adenocarcinoma; AS: adenosquamous carcinoma; CA/NOS: carcinoma not otherwise specified; FS: fibrosarcoma;
HA: hemangioma; HS: hemangiosarcoma; HA: hemangioma; HS: hemangiosarcoma; ME: mucoepidermoid tumor; NEC: neuroepithelial carcinoma; PAP: squamous cell papilloma; RM: rhabdomyoma; RS: rhabdomyosarcoma; SCC: squamous cell carcinoma; SCC: squamous cell carcinoma; UDC: undifferentiated carcinoma.
[c] Abbreviated nasal sites are as follows: BG: Bowman's gland; OE: olfactory epithelium; RE: respiratory epithelium; SG: submucosal gland; TE: transitional epithelium.
[d] Abbreviated lesions are as follows: ATR: atrophy; DEG: degeneration; DYS: dysplasia; HYP: hyperplasia; MET: metaplasia; NEC: necrosis.
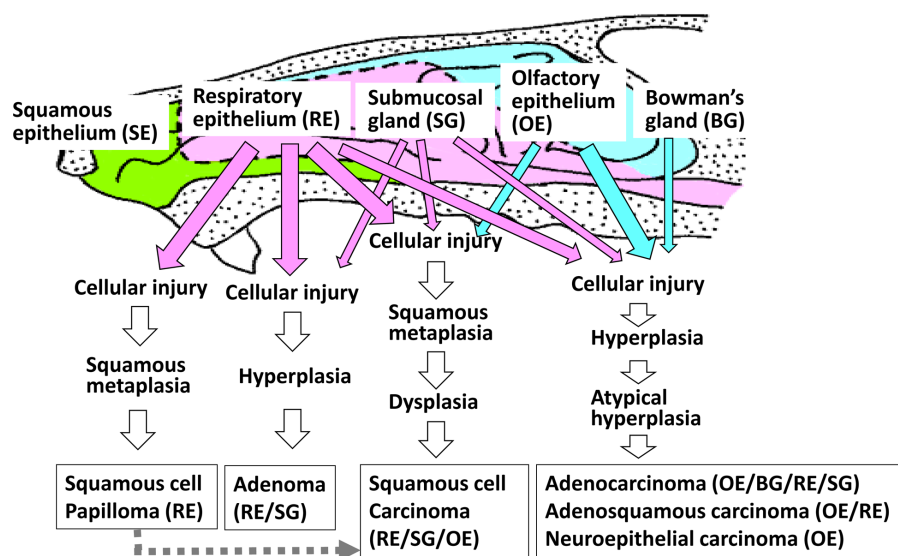[e] Abbreviations are as follows: A: Ames test; IV: *in vivo* tests.

Fig. 1. Possible pathways leading to nasal cavity tumors. SE: squamous epithelium; RE: respiratory epithelium; SG: submucosal gland; OE: olfactory epithelial; BG: Bowman's gland.

formaldehyde[14, 42, 49]. Dysplasia was found for 1,2-dibromo-3-chloropropane, formaldehyde, and phenyl glycidyl ether[32, 49, 72, 121, 122]. For 1,4-dioxane, degeneration, necrosis, desquamation, and inflammation were not evident in the RE; however, nuclear enlargement was observed in RE cells prior to squamous metaplasia[126]. For hexameth-

ylphosphoramide and phenyl glycidyl ether, findings similar to those for SE and RE were observed in the SG and NG. Thus, the pathway through which squamous cell carcinoma arises from the RE may involve degenerative and regenerative changes in the RE, followed by squamous hyperplasia, metaplasia, and dysplasia (Fig. 1).

Degenerative changes and subsequent squamous metaplasia were frequently observed in the OE pathway (Table 1). Furthermore, regeneration of the OE was reported for 1,2-dibromo-3-chloropropane and vinyl acetate[32, 79, 121, 122]. Thus, the pathway leading to squamous cell carcinoma may involve degenerative and regenerative changes in the OE, followed by squamous metaplasia and/or dysplasia (Fig. 1).

The following 16 substances have been reported to induce squamous cell carcinoma in rat non-inhalation studies (Supplementary Table 2): p-cresidine, diallylnitrosamine, dimethylvinyl chloride, 1,4-dioxane, N-nitrosodiethanolamine, N-nitrosodiethylamine, N-nitros-2,6-dimethylmorpholine, N-nitrosohexamethylenimine, N-nitrosomethyl-n-propylamine, 1-nitrosopiperazine, N-nitroso(2,2,2-trifluoroethyl)ethylamine, NNK, NNN, pentachlorophenol, phenacetin, and 2,3,7,8-TCDD. As shown in Tables 2 and 4, similar to the inhalation studies, squamous cell carcinoma appeared to develop from the RE in most cases. For dimethylvinyl chloride, the SG was another origin of squamous cell carcinoma. p-Cresidine, dimethylvinyl chloride, and 1,4-dioxane in the pathogenesis of squamous cell carcinoma were analyzed (Tables 2 and 3). As summarized in Fig. 1, the pathway leading to squamous cell carcinoma may involve nuclear enlargement in the RE, followed by squamous hyperplasia and metaplasia[127].

The following five substances have been shown to induce squamous cell carcinoma in mouse inhalation studies: butyl 2,3-epoxypropyl ether, 1,2-dibromo-3-chloropropane, formaldehyde, glycidol, and propylene oxide (Supplementary Table 1). In most cases, squamous cell carcinoma developed from the RE, similar to that observed in rat studies (Tables 1 and 4). Butyl 2,3-epoxypropyl ether, 1,2-dibromo-3-chloropropane, formaldehyde, and glycidol were evaluated for their roles in the pathogenesis of squamous cell carcinoma (Tables 1 and 3). Similar to rat studies, the pathway leading to squamous cell carcinoma may involve hyperplastic, metaplastic, and/or dysplastic changes in the RE (Fig. 1).

In a mouse non-inhalation study, N-nitrososarcosine was shown to induce squamous cell carcinoma (Supplementary Table 2), but its pathogenesis was not analyzed (Table 3). Dimethylcarbamoyl chloride, N-nitrosohexamethylenimine, and nitrosomorpholine have also been shown to induce squamous cell carcinoma in hamster inhalation and non-inhalation studies (Supplementary Tables 1 and 2); however, the pathogenic mechanisms of these compounds were not evaluated (Table 3).

Adenoma

The following 17 substances have been shown to induce adenomas in rat inhalation studies (Supplementary Table 1): allyl glycidyl ether, crotonaldehyde, cumene, 1,2-dibromo-3-chloropropane, 1,2-dibromoethane, 1,4-dichloro-2-butene, 1,2-epoxybutane, 2,3-epoxypropyl methacrylate, formaldehyde, furfuryl alcohol, glycidol, hexamethylphosphoramide, hydrazine, naphthalene, propargyl alcohol, propylene oxide, and N-vinyl-2-pyrrolidone. Adenomas were likely to have originated from the RE in most cases, from both the RE and the SG or NG for propylene oxide and N-vinyl-2-pyrrolidone, and from the TE as part of the RE for hydrazine (Tables 1 and 4). The pathogenic mechanisms of these 17 substances in adenomas were evaluated (Tables 1 and 3). Results showed that RE hyperplasia was commonly observed for all substances. Atrophic and/or necrotic changes in the RE were observed for all the four substances. Nuclear enlargement was evident with 1,2-dibromo-3-chloropropane, which may be an early step in the formation of adenocarcinoma rather than adenoma[32, 121, 122]. Thus, the pathway leading to adenoma is likely to involve atrophic and/or necrotic changes in the RE, followed by RE hyperplasia (including that in the TE and SG; Fig. 1).

The following seven substances induced adenomas in rat non-inhalation studies (Supplementary Table 2): p-cresidine, 2,3-dibromo-1-propanol, N-N-dimethyl-p-toluidine, NNK, NNN, phenacetin, and 2,6-xylidine. As shown in Tables 2 and 4, similar to the inhalation studies, adenomas appeared to develop from the RE or TE for all substances. The pathogenic mechanisms of four substances, p-cresidine, 2,3-dibromo-1-propanol, N-N-dimethyl-p-toluidine, and 2,6-xylidine, in adenoma were evaluated (Tables 2 and 3). The pathway leading to adenoma in the RE was suggested to involve hyperplasia of the RE, including the TE (Fig. 1).

The following eight substances have been shown to induce adenomas in mouse inhalation studies (Supplementary Table 1): acrolein, allyl glycidyl ether, 1,2-dibromo-3-chlo-

Table 3. Number of Chemical Substances Inducing Definite Nasal Cavity Tumors (with Available Data for Non-neoplastic Lesions)[a]

Tumors	Rat inhalation	Rat non-inhalation	Mouse inhalation	Mouse non-inhalation	Hamster inhalation	Hamster non-inhalation
Squamous cell papilloma	10 (10) [b]	8 (2)	4 (3)	0	0	5 (1)
Squamous cell carcinoma	23 (18)	17 (3)	5 (4)	1 (0)	1 (0)	2 (0)
Adenoma	17 (17)	7 (4)	8 (8)	1 (0)	1 (1)	6 (0)
Adenocarcinoma	13 (11)	16 (8)	5 (4)	1 (0)	0	5 (1)
Adenosquamous carcinoma	7 (4)	4 (1)	0	0	0	0
Neuroepithelial carcinoma	10 (7)	6 (2)	0	0	1 (0)	3 (0)
Mesenchymal tumor [c]	5 (5)	5 (3)	16 (11)	0	0	0

[a] Data are derived from Supplementary Tables 1 and 2, and Tables 1 and 2 (in bracket).
[b] Number of chemical substances (number of chemical substances with available data for non-neoplastic lesions).
[c] Rhabdomyoma, rhadomyosarcoma, hemangioma, hemangiosarcoma and fibrosarcoma are included.

ropropane, 1,2-dibromoethane, 2,3-epoxypropyl methacrylate, glycidol, propargyl alcohol, and propylene oxide. As shown in Tables 1 and 4, similar to rat studies, adenoma likely originated from the RE in most cases. For propargyl alcohol, adenoma may have originated from the TE. The pathogenic mechanisms of these eight substances in adenomas were evaluated (Tables 1 and 3). The pathway leading to adenoma in the RE has been suggested to involve RE or TE hyperplasia for all eight substances (Fig. 1). In a mouse oral study, N-nitrosohexamethyleneimine was shown to induce adenoma; however, its pathogenic mechanism could not be evaluated.

Hydrazine was the only substance shown to induce adenomas in hamster inhalation studies (Supplementary Table 1). The pathogenic mechanism in adenoma was evaluated (Table 3). As shown in Tables 1 and 4, similar to studies in rats and mice, adenomas appeared to originate from the RE or TE. The pathway leading to adenoma likely involves necrosis, desquamation, and hyperplasia of the RE or TE (Fig. 1).

Six substances have been shown to induce adenomas in hamster non-inhalation studies: N-nitrosomethyl-n-butylamine, N-nitrosomethyl-n-heptylamine, N-nitrosomethyl-n-hexylamine, N-nitrosomethyl-n-octylamine, N-nitrosomethyl-n-pentylamine, and N-nitrosomethyl-n-propylamine (Supplementary Table 2). However, no pathogenic mechanism was evaluated.

Adenocarcinoma

The following 13 substances induced adenocarcinoma in rat inhalation studies (Supplementary Table 1): acetaldehyde; bis(chloromethyl)ether; 1,2-dibromo-3-chloropropane; 1,2-dibromoethane; 1,4-dichloro-2-butene; 1,2,3,4-diepoxybutane; 2,3-epoxypropyl methacrylate; glycidol; hexamethylphosphoramide; hydrazine; 1-nitroso-4-methylpiperazine; vinyl chloride monomer, and N-vinyl-2-pyrrolidone. As shown in Tables 1 and 4, adenocarcinoma appeared to develop from the OE in most cases and from the RE or TE in some cases. For N-vinyl-2-pyrrolidone, adenocarcinoma may have arisen both the OE and BG (Table 1).

The pathogenic mechanisms of 11 of these substances, excluding bis(chloromethyl)ether and 1-nitroso-4-methylpiperazine, were evaluated in adenocarcinomas (Tables 1 and 3). Necrosis and/or atrophy of the OE was observed in response to 1,2-dibromo-3-chloropropane, 1,4-dichloro-2-butene, and N-vinyl-2-pyrrolidone. Enlargement of sustentacular and basal cells in the OE was evident only for 1,2-dibromo-3-chloropropane[32, 120, 121]. OE hyperplasia was observed after treatment with 1,4-dichloro-2-butene and N-vinyl-2-pyrrolidone. Hyperplasia induced by 1,4-dichloro-2-butene resembled epithelium-like cell clusters at the base and likely originated from basal cells in the OE[35]. Atypical hyperplasia of basal cells was noted for 1,4-dichloro-2-butene and vinyl chloride monomer[35, 81]. Thus, the pathway leading to adenocarcinoma likely involves necrosis and atrophy of the OE and/or enlargement of the sustentacular and basal cells (stem cells of sustentacular cells), followed

by hyperplasia and atypical hyperplasia of the basal cells (Fig. 1). Regarding the BG pathway, atrophy was observed for N-vinyl-2-pyrrolidone, hyperplasia was found for vinyl chloride monomer and N-vinyl-2-pyrrolidone, and atypical hyperplasia was evident for vinyl chloride monomer. Thus, the pathway leading to adenocarcinoma in the BG may involve atrophy, hyperplasia, and atypical hyperplasia of the BG (Fig. 1).

The following 15 substances induced adenocarcinoma in non-inhalation rat studies: *p*-cresidine, diallylnitrosamine, 2,3-dibromo-1-propanol, N-N-dimethyl-*p*-toluidine, dimethylvinylchloride, 1,4-dinitrosopiperazine, 1,4-dioxane, N-nitrosodiethanolamine, N-nitros-2,6-dimethylmorpholine, N-nitrosohexamethylenimine, 1-nitroso-4-methylpiperazine, 1-nitrosopiperidine, NNN, phenacetin, and 2,6-xylidine (Supplementary Table 2). As shown in Tables 2 and 4, in most cases, adenocarcinoma appeared to develop from the OE and/or RE. For *p*-cresidine, both BG in OE and the SG, or NG in the RE, may also be the origin of adenocarcinoma. The pathogenic mechanisms of eight substances, *p*-cresidine, 2,3-dibromo-1-propanol, N-N-dimethyl-*p*-toluidine, dimethylvinylchloride, 1,4-dinitrosopiperazine, 1,4-dioxane, N-nitrosomethylpiperazine, and 2,6-xylidine, were evaluated in adenocarcinomas (Tables 2 and 3). In the OE pathway, degeneration was observed for N-nitrosomethylpiperazine, hyperplasia was found for 1,4-dinitrosopiperazine and N-nitrosomethylpiperazine, and atypical hyperplasia of the columnar and sustentacular cells was noted for N-nitrosopiperidine. Thus, the pathway leading to adenocarcinoma in the OE may involve degeneration of the OE, followed by hyperplasia or atypical hyperplasia of the columnar and sustentacular cells (Fig. 1). The pathogenic mechanisms for adenocarcinoma from BG were analyzed in studies of *p*-cresidine, diallylnitrosamine, phenacetin, and 2.6-xylidine. In the BG or NG pathways, necrosis and inflammation were observed for phenacetin[128] and 2,6-xylidine, and hyperplasia of BG was observed for *p*-cresidine, diallylnitrosamine, and 2,6-xylidine. Thus, the pathway leading to adenocarcinoma may involve necrosis, inflammation, and hyperplasia of BG (Fig. 1). Similarly, the pathway leading to adenocarcinoma in the NG was analyzed only for *p*-cresidine and was suggested to be hyperplasia of the NG (Fig. 1).

Five substances were found to induce adenocarcinoma in mouse inhalation studies: 1,2-dibromo-3-chloropropane, 1,2-dibromoethane, 2,3-epoxypropyl methacrylate, glycidol, and propylene oxide (Supplementary Table 1). As shown in Tables 1 and 4, similar to the rat studies, adenocarcinoma developed in the OE or NG in the RE. The pathogenic mechanisms of four of these substances, excluding propylene oxide, were analyzed in adenocarcinomas (Tables 1 and 3). Atrophic or degenerative changes, followed by metaplastic changes in the affected cells, may lead to adenocarcinoma, although the data are limited (Fig. 1). In a mouse oral study, N-nitrosohexamethyleneimine induced adenocarcinoma; however, the pathogenic mechanism in adenocarcinoma was not evaluated.

N-nitrosodiethanolamine, N-nitrosodiethylamine, N-nitros-2,6-dimethylmorpholine, N-nitrosohexamethylenimine, and nitrosomorpholine were found to induce adenocarcinoma in hamster non-inhalation studies (Supplementary Table 2). The pathogenic mechanism of N-nitros-2,6-dimethylmorpholine in adenocarcinoma was analyzed, and hyperplastic or metaplastic lesions were noted in the RE cells (Table 2 and Fig. 1).

Adenosquamous carcinoma

Seven substances were found to induce adenosquamous carcinoma in rat inhalation studies: butyl 2,3-epoxypropyl ether, 1,4-dichloro-2-butene, 2,3-epoxypropyl methacrylate, hexamethylphosphoramide, N-nitrosodimethylamine, N-nitrosomethylpiperazine, and nitrosomorpholine (Supplementary Table 1). Mucoepidermoid carcinoma, identified in a study on N-nitrosodimethylamine, was included as a type of adenosquamous carcinoma. As shown in Tables 1 and 4, adenosquamous carcinoma appeared to develop from the RE and OE. As shown in Tables 1 and 3, the pathogenic mechanisms of butyl 2,3-epoxypropyl ether, 1,4-dichloro-2-butene, 2,3-epoxypropyl methacrylate, and hexamethylphosphoramide in adenosquamous carcinoma were assessed[27, 35, 57]. The pathway leading to adenosquamous carcinoma in the RE may involve the degeneration and desquamation of ciliated and goblet cells of the RE, as well as primitive adenomatoid cells (Fig. 1).

The following four substances induced adenosquamous carcinoma in non-inhalation studies in rats (Supplementary Table 2): diallylnitrosamine, 1,4-dinitrosopiperazine, N-nitrosodimethylamine, and N-nitroso(2,2,2-trifluoroethyl)ethylamine. As shown in Tables 2 and 4, adenosquamous carcinoma appeared to have originated from the OE. As shown in Tables 2 and 3, only the pathogenic mechanism of 1,4-dinitrosopiperazine in adenosquamous carcinoma was evaluated[93]. The pathway leading to adenosquamous carcinoma in the OE may involve nodular hyperplasia, although the data are limited (Fig. 1).

Neuroepithelial carcinoma

The following ten substances induced neuroepithelial carcinoma in rat inhalation studies: allyl glycidyl ether, bis(chloromethyl)ether, butyl 2,3-epoxypropyl ether, 1,2-dichloropropane, 1,4-dioxane, 2,3-epoxypropyl methacrylate, naphthalene, N-nitrosodimethylamine, 1-nitroso-4-methylpiperazine, and vinyl chloride monomers (Supplementary Table 1). The OE was the likely origin in most cases (Tables 1 and 4). The pathogenic mechanisms of seven substances (allyl glycidyl ether, butyl 2,3-epoxypropyl ether, 1,2-dichloropropane, 1,4-dioxane, 2,3-epoxypropyl methacrylate, naphthalene, and vinyl chloride monomers) in neuroepithelial carcinoma were evaluated (Tables 1 and 3). The pathway leading to neuroepithelial carcinoma is suggested to involve inflammatory and atrophic changes in the OE, followed by atypical hyperplasia and neuroepithelial carcinoma[27] (Fig. 1).

Six substances induced neuroepithelial carcinoma in rat non-inhalation studies (Supplementary Table 2): p-cresidine, 1,4-dioxane, N-nitrosodiethanolamine, 1-nitrosopiperazine, NNK, and NNN. As shown in Tables 2 and 4, similar to the inhalation studies, the origin may be the OE. As shown in Tables 2 and 3, the pathogenic mechanisms of p-cresidine and 1,4-dioxane in neuroepithelial carcinoma were evaluated[86, 95], and the pathway may begin with inflammatory and atrophic changes, followed by atypical hyperplastic lesions (Fig. 1).

In hamster studies (Supplementary Tables 1 and 2), nitrosomorpholine induced neuroepithelial carcinoma by both inhalation and non-inhalation exposure, and N-nitrosohexamethylenimine and NNN induced neuroepithelial carcinoma by non-inhalation exposure; the pathogenic mechanisms of these compounds were not evaluated for neuroepithelial carcinoma (Table 4).

Mesenchymal tumors

Crotonaldehyde, 1,4-dichloro-2-butene, and 1,4-dioxane induced rhabdomyosarcoma in the rat inhalation studies, whereas dimethylvinylchloride, 1,4-dioxane, NNK, NNN, and 2,6-xylidine induced rhabdomyosarcoma in the non-inhalation studies (Supplementary Tables 1 and 2). The pathogenic mechanisms of crotonaldehyde, 1,4-dichloro-2-butene, dimethylvinylchloride, 1,4-dioxane, and 2,6-xylidine in rhabdomyosarcoma were evaluated (Tables 1 and 2). However, non-neoplastic lesions in striated muscles have rarely been recorded, and rhabdomyoma was induced only in a rat inhalation study of acrolein[18] (Table 1).

Allyl glycidyl ether, butyl 2,3-epoxypropyl ether, 2,3-epoxypropyl methacrylate, glycidol, and propylene oxide induced hemangioma in mouse inhalation studies (Supplementary Table 1), and pathogenic analyses of these five substances in hemangioma were performed (Tables 1 and 3). The tissue from which the hemangioma developed may have been of blood vessel origin, and the initial pathway leading to hemangioma in the blood vessels may involve dilation of the blood vessels below the RE, followed by hemangioma.

In mouse inhalation studies (Supplementary Table 1), 1,2-dibromo-3-chloropropane, 2,3-epoxypropyl methacrylate, glycidol, and propylene oxide induced hemangiosarcoma, possibly of blood vessel origin. The pathogenic mechanisms of four of these substances, excluding propylene oxide, were evaluated in hemangiosarcoma (Table 1). Similar to hemangioma, the initial pathway leading to hemangiosarcoma is the dilation of blood vessels below the RE.

1,2-Dibromo-3-chloropropane was the only substance known to induce fibrosarcoma in a mouse inhalation study (Supplementary Table 1), and its pathogenic mechanism was assessed (Table 1). However, non-neoplastic lesions of mesenchymal origin have rarely been reported.

Comparison of nasal cavity tumors by rodent species

Twelve substances induced nasal cavity tumors with definite histopathological types in different rodent species exposed to inhalation (Table 5). Among these compounds, 1,2-dibromo-3-chloropropane, 1,2-dibromoethane, 2,3-ep-

Table 4. Possible Origin of Nasal Cavity Tumors

Tumors	Rat inhalation	Rat non-inhalation	Mouse inhalation	Hamster inhalation	Hamster non-inhalation
Squamous cell papilloma	RE [a]	RE	RE	NA [b]	RE
Squamous cell carcinoma	RE/SG/OE	RE/SG	RE/OE	NA	NA
Adenoma	RE/SG	RE	RE/SG	RE	NA
Adenocarcinoma	OE/BG/RE	OE/BG/RE/SG	OE/RE/SG	NA	OE
Adenosquamous carcinoma	OE/RE	OE	NA	NA	NA
Neuroepithelial carcinoma	OE	OE	NA	NA	NA

[a] Abbreviated nasal sites are as follows: BG: Bowman's gland; NG: nasal gland; OE: olfactory epithelium; RE: respiratory epithelium; SE: squamous epithelium; SG: submucosal gland; TE: transitional epithelium.
[b] NA: not addressed.

Table 5. Comparison of Nasal Cavity Tumors by Rodent Species Exposed to Inhalation

Chemical substances	Species	Nasal cavity tumors[a] (sites[b])
acrolein	rat	SCC; RM
	mouse	AD
allyl glycidyl ether	rat	AD (RE); NEC (OE); SCC (RE)
	mouse	AD (RE), HA
butyl 2,3-epoxypropyl ether	rat	PAP; SCC; NEC; AS
	mouse	HA; SCC
1,2-dibromo-3-chloropropane	rat	AD (RE); ADC (OE); PAP (RE); SCC (RE/OE)
	mouse	PAP (RE); SCC, AD (RE); ADC, HS, FS (OE)
1,2-dibromoethane	rat	AD; ADC; SCC; CA/NOS
	mouse	PAP (RE); AD (RE); SCC (OE); ADC (OE); HS
2,3-epoxypropyl methacrylate	rat	AD; ADC; AS; PAP; SCC; NEC; HS
	mouse	AD; ADC; HS; HA
formaldehyde	rat	PAP (RE); SCC (RE); AD (RE/TE)
	mouse	SCC
glycidol	rat	SCC (RE/TE); AD (RE/TE); ADC (RE/TE)
	mouse	HA; HS; AD/ADC (RE/NG); PAP, SCC (RE)
hydrazine	rat	PAP, SCC, AD (RE/TE); ADC
	hamster	AD (RE/TE)
nitrosomorpholine	rat	AS
	hamster	NEC
propargyl alcohol	rat	AD (RE/TE)
	mouse	AD (RE/TE)
propylene oxide	rat	AD
	mouse	HA; HS; ADC; SCC; PAP

[a] Abbreviated tumor types are as follows: AD: adenoma; ADC: adenocarcinoma; AS: adenosquamous carcinoma; FS: fibrosarcoma; HA: hemangioma; HS: hemangiosarcoma; ME: mucoepidermoid tumor; NEC: neuroepithelial carcinoma; PAP: squamous cell papilloma; RM: rhabdomyoma; RS: rhabdomyosarcoma; SCC: squamous cell carcinoma.
[b] Abbreviated nasal sites are as follows: OE: olfactory epithelium; RE: respiratory epithelium; SG: submucosal gland; TE: transitional epithelium.

oxypropyl methacrylate, glycidol, nitrosomorpholine, and propargyl alcohol induced roughly similar histological types of tumors; allyl glycidyl ether, butyl 2,3-epoxypropyl ether, formaldehyde, and hydrazine induced partly similar histological types; but acrolein and propylene oxide induced different histological types in rodent species. Interestingly, 2,3-epoxypropyl methacrylate induced hemangiomatous tumors in both rats and mice.

Comparison of nasal cavity tumors by exposure routes

Among six substances exposed to the same rodent species via both inhalation and non-inhalation routes 1,4-di-oxane, N-nitrosodimethylamine, 1-nitoroso-4-methylpiperazine, and nitrosomorpholine all induced nasal cavity tumors with definitive histopathological typing. As shown in Table 6, the histological types of the induced tumors were similar for these four substances, suggesting that the nasal cavity tumors generated by inhalation exposure may be caused by local and systemic effects. For example, 1,4-di-oxane induced squamous cell carcinoma, neuroepithelial carcinoma, and rhabdomyosarcoma via both the inhalation and oral routes. Adenosquamous carcinoma was induced by N-nitrosodimethylamine, adenocarcinoma was induced by 1-nitroso-4-methylpiperazine, and neuroepithelial carcinoma was induced by nitrosomorpholine via both inhalation

Table 6. Comparison of Nasal Cavity Tumors by Exposure Routes

Chemical substances	Species	Exposure	Nasal cavity tumors[a]
1,4-dioxane	rat	inhalation	SCC, RS, NEC
		oral	SCC, ADC, NEC, RS
N-nitrosodimethylamine	rat	inhalation	NEC, AS, SCC
		ip injection	AS
1-nitroso-4-methylpiperazine	rat	inhalation	AS, ADC, NEC
		oral	ADC
nitrosomorpholine	hamster	inhlation	NEC
		sc injection	PAP, SCC, ADC, NEC

[a] Abbreviated tumor types are as follows: ADC: adenocarcinoma; AS: adenosquamous carcinoma; NEC: neuroepithelial carcinoma; PAP: squamous cell papilloma; RS: rhabdomyosarcoma; SCC: squamous cell carcinoma.

and non-inhalation routes.

Genotoxicity of chemicals inducing nasal cavity tumors

Among the 37 substances (excluding 1,4-dioxane) for which the pathogenesis of nasal cavity tumors in rodent studies was analyzed (Tables 3 and 4), 26, 2, and 9 were positive, equivocal, and negative on Ames tests, respectively. In the Ames tests, acrolein and hexamethylphosphoramide were equivocal or weakly positive substances; however, both were positive in *in vivo* genotoxicity tests, including *in vivo* micronucleus and chromosomal aberration tests[13, 15]. In Ames tests, acetaldehyde, cumene, N,N-dimethyl-*p*-toluidine, 1,4-dioxane, furfuryl alcohol, methyl acrylate, naphthalene, vinyl acetate, and N-vinyl-2-pyrrolidone were negative, and among these substances, four, three, and two substances were positive, equivocal, and negative, respectively, in *in vivo* genotoxicity studies. Acetaldehyde was positive in *in vitro* sister chromatid exchange tests with human lymphocytes and CHO cells, gene mutation tests with human lymphocytes, and chromosomal aberration tests with human lymphocytes, and has been reported to cause DNA-protein crosslinks in the rat nasal mucosa *in vivo*[15]. Cumene tested positive in *in vivo* micronucleus tests in the bone marrow of male rats (via peritoneal administration)[29, 30]. N,N-Dimethyl-*p*-toluidine was positive in *in vitro* mouse lymphoma Tk tests and chromosomal aberration tests and induced DNA damage in rat livers[61, 91]. 1,4-Dioxane was positive in *in vitro* cell transformation tests, but equivocal in *in vivo* genotoxicity tests[15]. Furfuryl alcohol was positive in sister chromatid exchange tests with CHO cells, but negative in *in vivo* genotoxicity tests[53, 116]. Methyl acrylate was equivocal in *in vivo* genotoxicity tests[54]. Naphthalene was positive in *in vitro* sister chromatid exchange and chromosomal aberration tests[64, 67]. Vinyl acetate was positive in *in vitro* micronucleus tests, chromosomal aberration tests, and *in vivo* micronucleus tests and has been reported to cause DNA-protein crosslinks *in vitro* in RE and OE cells of the rat nasal cavity[80, 129]. N-Vinyl-2-pyrrolidone was consistently negative in the Ames tests and mouse micronucleus tests[15, 130]. Thus, furfuryl alcohol and N-vinyl-2-pyrrolidone, which showed negative results in both the Ames and *in vivo* genotoxicity

tests, were considered non-genotoxic carcinogens targeting the nasal cavity. Importantly, adenoma and squamous cell carcinoma induced by furfuryl alcohol, and adenoma and adenocarcinoma induced by N-vinyl-2-pyrrolidone, showed similar pathogenic mechanisms to those of most other genotoxic substances.

Discussion

In this report, data for chemically-induced nasal cavity tumors in rodents were comprehensively surveyed. After standardizing the nomenclature of neoplastic and non-neoplastic nasal cavity lesions, the pathogenic mechanisms of different types of nasal cavity tumors were assessed. In addition, it was difficult to estimate the tumorigenic pathway using only coexisting or preexisting lesions found in studies of carcinogenicity. Therefore, to reinforce the data from acute or short-term studies, some related references have also been discussed.

As summarized in Table 6, squamous cell papilloma, squamous cell carcinoma, and adenoma may originate from the RE in most cases, and from the OE or SG in some cases. Since squamous cell papilloma and carcinoma are likely sequential neoplastic changes that occur with the progression from benign to malignant tumors, it is reasonable that the original tissues and developing pathways may largely overlap[131]. In contrast, adenocarcinoma, adenosquamous carcinoma, and neuroepithelial carcinoma may originate from the OE in most cases and from the RE, BG, or SG in some cases. These results were independent of the species and exposure route. Although sequential changes from adenoma to adenocarcinoma have been suggested in human cases[132], the current analysis indicated that this sequence was minor, suggesting that *de novo* development of adenocarcinoma was predominant in rodent cases. Plausible pathways for tumor development for each histological type are summarized in Fig. 1. Regardless of the cells of origin, the pathogenic mechanisms leading to nasal cavity tumors appear to be comparable. The initial step involves cytotoxic changes such as necrosis, degeneration, desquamation, and inflammation, and the subsequent step involves regenerative changes such as hyperplasia, metaplasia, and dysplasia.

In association with metabolic studies[133–135], degeneration and necrosis of RE cells in the nasal cavity were histopathologically identified in rodents briefly exposed to formaldehyde by inhalation[123, 124, 136–139]. These changes were evident after 6 h of exposure[123]. In a study in which F344 rats and B6C3F$_1$ mice were exposed to formaldehyde by inhalation for 6 h, early degeneration and sloughing of the RE in the nasal cavity was observed in animals sacrificed immediately after exposure[123]. Although RE degeneration has also been observed in mice, the effect was milder than that in rats[123]. Moreover, transmission electron microscopy revealed cytoplasmic vacuolization of the entire RE, loss of microvilli in the ciliated RE, and autophagic vacuolization of basal cells in the nasal cavity of F344 rats sacrificed immediately following exposed to formaldehyde by inhalation for 6 h[136]. Additionally, in a study on Wistar rats exposed to formaldehyde by inhalation for 6 h/day for 3 days, deciliation of the RE in the nasal cavity was observed in some animals[124]. In a study of F344 rats exposed to formaldehyde by inhalation for 6 h/day, vacuolar degeneration of epithelial cells, individual cell necrosis, epithelial exfoliation, and erosion occurred in the RE of the anterior nasal passages after 1 day of exposure[139]. Similar observations were reported for acetaldehyde[140], 1,2-dibromoethane[122, 141], 1,4-dioxane[126, 127], phenacetin[142], and vinyl acetate[143].

In male and female Wistar rats exposed to concentrations of up to 20 ppm formaldehyde vapor for 6 h/day, 5 days/week for 13 weeks, keratinized stratified squamous metaplasia of the nasal RE and focal degeneration and squamous metaplasia occasionally accompanied by keratinization of the OE were observed in a treatment-related manner[144] In addition, an *in vivo/in vitro* cell proliferation study showed an increase in the [3H]-thymidine labeling index of the RE lining the nasoturbinates of rats exposed to formaldehyde on three successive days[144]. Similarly, in male Wistar rats exposed to formaldehyde for 13 weeks, 5 days/week at 1 or 2 ppm continuously (8 h/day), or at 2 or 4 ppm periodically, the degree and incidence of squamous metaplasia increased, accompanied by basal cell hyperplasia and keratinization of the RE in the nose of animals exposed to 4 ppm formaldehyde[145]. These findings suggest that under repeated exposure to marginally cytotoxic concentrations over a period of 13 weeks, the exposure concentration, rather than the total dose, may determine the severity of the cytotoxic effects of formaldehyde on the nasal epithelium[145]. In the current study, similar observations were made for various chemical substances that induce squamous cell carcinoma in the rodent nose.

The pathogenesis of squamous metaplasia has been analyzed using transmission electron microscopy[57, 58]. In squamous metaplasia induced in the RE of rats exposed to hexamethylphosphoramide by inhalation, after degeneration and desquamation of ciliated cells and goblet cells, repair with primitive mucous cells and cuboidal cells with microvilli occurred, followed by replacement with squamous cells from the basal side to the upper side, resulting in squamous metaplasia accompanied by keratinization[57, 58]. This demonstrates the utility of electron microscopy for analyzing pathogenesis based on detailed ultrastructural changes.

Transmission electron microscopy of rats exposed to 1,2-dibromo-3-chloropropane by inhalation showed that the pathogenesis of adenocarcinoma begins with cell damage such as necrosis and atrophy of basal cells in the OE, BG, or SG, followed by hyperplasia or atypical hyperplasia[121]. These findings were noted regardless of the route of administration of many substances in the current survey[121]. For the pathogenesis of adenosquamous carcinoma, transmission electron microscopy revealed that after degeneration or desquamation of ciliated and goblet cells in the RE of rats exposed to hexamethylphosphoramide, primitive adenomatoid cells, which have the potential to differentiate into both adenomatoid cells and squamous cells, appeared above the basal membrane. Thus, adenosquamous carcinoma may have arisen from intermediate cells following primitive cells[57]. Nodular hyperplasia of these cells may also be involved in the development of adenosquamous carcinoma from the OE induced by 1,4-dinitrosopiperazine[93].

Species differences in nasal cavity tumorigenesis have been previously reviewed in the NTP database to unify terminology and compare induced and spontaneous tumors and hyperplastic or preneoplastic lesions produced in the nose[146]. The species affected, administration route, and tumor types produced by the different chemicals were also compared. In the current analysis, rats were more susceptible to epithelial tumors of the nasal cavity than mice, which is consistent with a previous report[146]. Hemangiomatous tumors were also rarely induced in rats, which is somewhat different from a previously reported finding that hemangiomatous tumors were induced only in mice[146]. Furthermore, most chemically induced tumors of the olfactory region have been suggested to not require inhalation exposure, but rather systemic targeting of this region[146]. However, in this study, we found that nasal cavity tumors mainly originated from the OE and formed adenocarcinoma, adenosquamous carcinoma, and neuroepithelial carcinoma following both inhalation and non-inhalation exposure.

Inhalation-specific toxicology limits have been derived for acrolein, formaldehyde, and methyl bromide due to their localized toxicity when administered via inhalation[147]. Thus, it is likely that several compounds previously have been incorrectly evaluated to be mutagenic carcinogens, whereas they may have a non-mutagenic mode of action in tumor induction[147]. However, the histological types of tumors induced by the four substances with both inhalation and non-inhalation exposure were similar, regardless of the exposure route, suggesting that nasal cavity tumors in rodents exposed to inhalation may be caused not only by local effects but also by systemic effects. In contrast, non-inhalation-related regurgitation or reflux may be a potential mechanism for promoting nasal tumorigenesis[148, 149].

In human sinonasal tumors, mutations in genes such as *KRAS*, *APC*, and *STK11* accumulate significantly in the order of inverted papilloma < dysplasia < squamous cell carcinoma, and *TP53* may be involved in malignant transfor-

mation based on the mutation site[131]. Although some human sinonasal tumors may be caused by the human papilloma virus[150], occupational chemical exposure may also be involved in human nasal tumor cases[151]. These data suggest that squamous cell papilloma and carcinoma represent sequential neoplastic changes that progress from benign to malignant.

In the current survey, furfuryl alcohol and N-vinyl-2-pyrrolidone were found to be similar to non-genotoxic carcinogens targeting the nasal cavity, based on the negative results obtained in both the Ames and *in vivo* genotoxicity tests. Importantly, in comparison to most genotoxic carcinogens, the pathology leading to nasal cavity tumors, that is, squamous cell carcinoma or adenocarcinoma, was quite similar, regardless of genotoxicity. This evidence suggests that subsequent post-genotoxic pathways toward nasal cavity tumorigenesis may largely overlap for genotoxic and non-genotoxic carcinogens. Notably, nasal cavity toxicants do not always induce tumors[149, 152].

The shift in the toxicity and carcinogenicity assessments of environmental chemicals from animal studies to *in vitro* and *in silico* tests is inevitable[153]. Artificial intelligence (AI) techniques may replace animal testing for unknown chemical substances. However, it is still important to efficiently and precisely utilize existing animal data. In particular, the nasal cavity mucosa has the second highest metabolic activity, after the liver; therefore, data for chemically induced nasal cavity tumors could be important sources[154]. Thus, critical and comprehensive reviews of animal carcinogenicity data, other than nasal cavity tumors, may be helpful in facilitating the progression of AI approaches.

Conclusions

Based on the current critical literature review of nasal cavity tumors induced in rodents, the major pathogenic mechanisms leading to nasal cavity tumors in rodents are summarized in Fig. 1. The data show that squamous cell papillomas and carcinomas mainly develop through squamous metaplasia following cell damage during RE. Substances that induce squamous cell carcinoma are often associated with hyperplastic and/or dysplastic lesions. Adenomas mainly develop through hyperplasia following cell damage in the RE; however, adenocarcinomas mainly develop through hyperplasia and/or atypical hyperplasia following cell damage in the OE. Similar to adenocarcinoma, adenosquamous carcinoma also develops through hyperplastic lesions in the OE, suggesting that adenosquamous carcinoma is a type of adenocarcinoma. Neuroepithelial carcinoma develops through inflammation and atrophy in the OE, followed by atypical hyperplasia. Except for hemangiomatous tumors, which may develop through dilatation of blood vessels, data on most mesenchymal tumors are limited. The pathogenesis of each type of nasal cavity tumor was similar regardless of genotoxicity, animal species, or exposure route, suggesting that the subsequent pathways toward tumorigenesis largely overlap between genotoxic and non-genotoxic carcinogens. IATAs for non-genotoxic carcinogens may not address different approaches from genotoxic carcinogens, suggesting that IATAs may be more practical for carcinogens in general than for only non-genotoxic carcinogens, at least for nasal cavity tumors.

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