

**90-day Brake Dust Sub-chronic Inhalation Toxicology Study (Nose-only) in the Rat  
(CiToxLAB study code: 15/248-212P; Fraunhofer ITEM Study No.: 02G16015)  
Pathology Phase-Report, Draft 1**

---

Lungs

a) Neoplastic findings

Tumors within the lung were detected in the groups clean air (one tumor), brake dust high (one tumor), titanium dioxide (one tumor), Chrysotile low (one tumor), Crocidolite (five tumors), and Amosite (nine tumors). These consisted of malignant tumors in one animal of group brake dust high (this animal had two bronchiolo-alveolar carcinomas), one malignant tumor in group titanium dioxide (bronchiolo-alveolar carcinoma), three malignant tumors in group Crocidolite (all bronchiolo-alveolar carcinomas), and four malignant tumors in group Amosite (three bronchiolo-alveolar carcinomas and one adenocarcinoma) and benign bronchiolo-alveolar adenomas in group clean air (one adenoma), Chrysotile low (one adenoma), Crocidolite (one adenoma and one adenoma with atypia), and Amosite (four adenomas and one adenoma with atypia). In addition, there were preneoplastic bronchiolo-alveolar hyperplasias of the alveolar type with atypia (hyperplasia of pneumocytes type 2) in the groups clean air (one), brake dust low (one), brake dust high (two), Chrysotile high (one), Crocidolite (four), and Amosite (three). One of the three animals of the Amosite group with the bronchiolo-alveolar hyperplasias of the alveolar type with atypia had two of these lesions. Bronchiolo-alveolar hyperplasias of the alveolar type without atypia (hyperplasia of pneumocytes type 2) were observed in the groups clean air (one), brake dust low (five), brake dust mid (one), brake dust high (four), titanium dioxide (three), Chrysotile low (four), Chrysotile high (seven), Crocidolite (eight), and Amosite (six). Bronchiolo-alveolar hyperplasias of the alveolar type were only diagnosed if they were not correlated to spontaneous alveolar macrophage aggregation.

Bronchiolo-alveolar hyperplasias of the bronchiolar type (bronchiolization) were diagnosed as “hyperplasia, bronchiolo-alveolar”. This findings is interpreted to be an adaptive change and is discussed in the next chapter.

Metastases into the lung of primary tumors outside the respiratory tract were seen in one animal of group 1 (clean air; carcinoma of the thyroid gland), one animal of group 2 (brake dust low; carcinoma of the thyroid gland), in one animal of group 9 (Amosite; carcinoma of the adrenal gland), and in one animal of group 9 (Amosite; carcinoma of the liver). In one animal of group 4 (brake dust high) metastases from an organ outside the respiratory tract

		Group				
		1	2	3	4	5
		Clean air	Brake dust low	Brake dust mid	Brake dust high	Titaniumdioxide
Malignant tumors	Carcinoma, bronchiolo-alveolar	0	0	0	1	1
	Adenocarcinoma	0	0	0	0	0
Benign tumors	Adenoma, bronchiolo-alveolar with atypia	0	0	0	0	0
	Adenoma, bronchiolo-alveolar	1	0	0	0	0
Hyperplasia	bronchiolo-alveolar, alveolar type with atypia	1	1	0	2	0
	bronchiolo-alveolar, alveolar type	1	5	1	4	3
	bronchiolo-alveolar (bronchiolar type)	0	0	2	4	3

**90-day Brake Dust Sub-chronic Inhalation Toxicology Study (Nose-only) in the Rat  
(CiToxLAB study code: 15/248-212P; Fraunhofer ITEM Study No.: 02G16015)  
Pathology Phase-Report, Draft 1**

---

were detected, of which the origin remained unknown (primary site unknown) since no malignant tumor was seen on the slides provided. One animal of group 4 (brake dust high) showed an infiltration of the lung by lymphoma cells. The metastases and the lymphoma were interpreted to be incidental without any relation to the treatment.

		Group			
		6	7	8	9
		Chrysotile low	Chrysotile high	Crocidolite	Amosite
Malignant tumors	Carcinoma, bronchiolo-alveolar	0	0	3	3
	Adenocarcinoma	0	0	0	1
Benign tumors	Adenoma, bronchiolo-alveolar with atypia	0	0	1	1
	Adenoma, bronchiolo-alveolar	1	0	1	4
Hyperplasia	bronchiolo-alveolar, alveolar type with atypia	0	1	4	3
	bronchiolo-alveolar, alveolar type	4	7	8	6
	bronchiolo-alveolar (bronchiolar type)	6	20	31	31

b)

**Macroscopically suspected visceral pleural lesions in the lung**

Within the animals 8070, 8073, 8082, 8097, 9071, 9073, 9080, 9085, 9087, 9090, 9092, 9094, 9096, 9097, 9098, and 9171 macroscopically changes of the lung were suspected to be visceral pleural lesions. The macroscopic changes correlated with bronchiolo-alveolar carcinoma, bronchiolo-alveolar adenoma or bronchiolo-alveolar hyperplasia (alveolar type with atypia) in the lung parenchyma. The lesions in the overlying lung visceral pleura consisted of (multi)focal very slight to slight mesothelial (visceral pleural) hyperplasias and/or pleural fibrosis. One animal, animal 9097, showed an adhesion of the lung pleura to the thoracic wall. All of these pleural lesions were interpreted to be a consequence of the respective lung parenchymal lesions. Further, due to the mild extent (very slight to slight) of the pleural lesions, they were unlikely to have caused the macroscopically visible changes alone.