

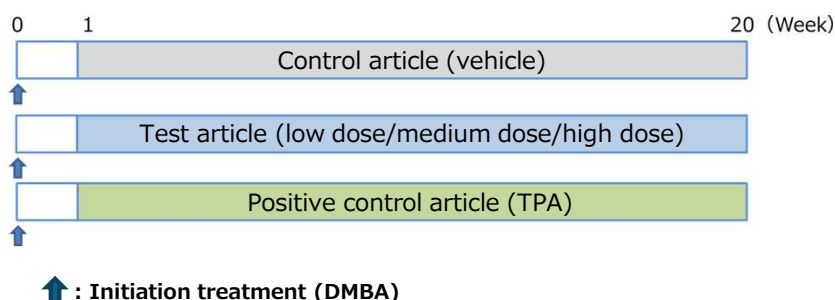


Medium-term skin carcinogenicity test

Purpose of this study is to predict the skin carcinogenicity of test articles using 7,12-dimethylbenz[a]anthracene (DMBA). This test has been used as an alternative to long-term carcinogenicity studies by adding transdermal patch or topical formulations to an existing oral formulation, and is used in applications to the Pharmaceuticals and Medical Devices Agency (PMDA).

Test Method

Schedule



Animals used: Female Crl:CD1 (ICR) mice

Initiator: 7,12-Dimethylbenz[a]anthracene (DMBA)
(Dosage: 100 µg/mouse, transdermal administration)

Positive control article: 12-O-tetradecanoylphorbol-13-acetate (TPA)
(Dosage: 4 µg/mouse, transdermal administration, twice a week)

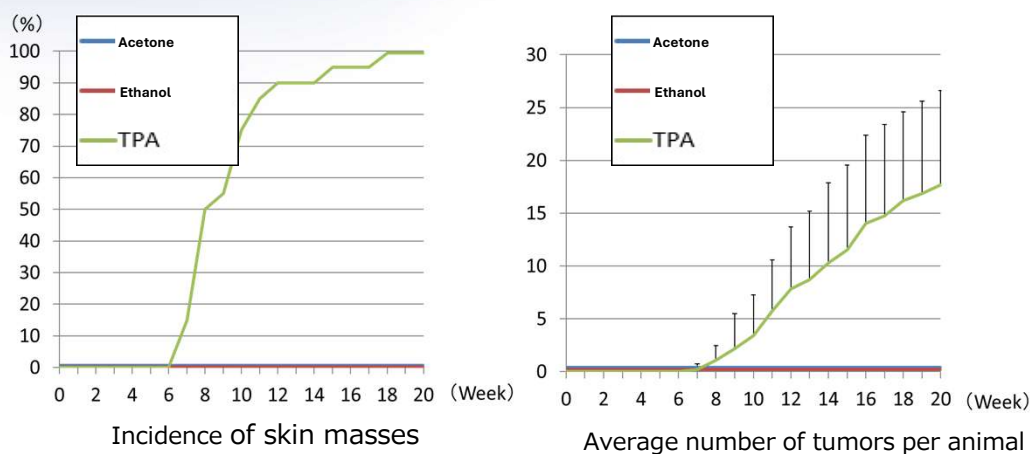
Test method: After shaving the hair over the dorsum, 100 µg of DMBA is administered once to the back skin. The test article is administered transdermally daily for 19 weeks from 1 week after DMBA administration.

Evaluation and Results

Evaluation items: Observation of skin tumors (number, size), histopathological examination

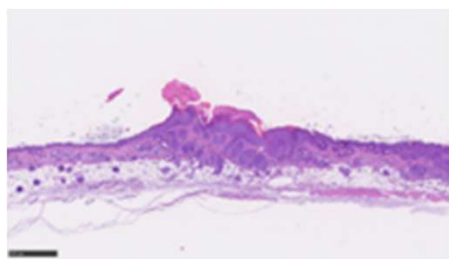
Evaluation method: During the housing period, the number of skin tumors is counted over time, and the number and incidence of tumors in each group are calculated and evaluated. After necropsy, histopathological examination of the skin is performed.

Measurement of skin tumors

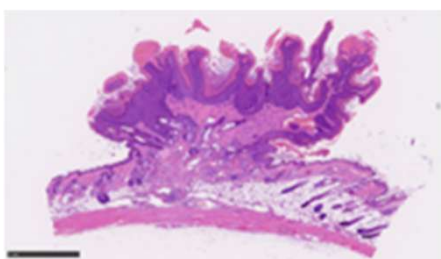


Incidence and average number of skin tumors

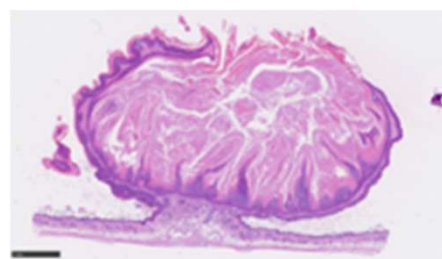
Histopathological examination



Epidermal hyperplasia



Squamous papilloma



Keratoacanthoma

Group	Acetone	Ethanol	TPA	Group	Epidermal hyperplasia	Squamous papilloma	Keratoacanthoma
Finding				Acetone	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Normal	100	100	0	Ethanol	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Epidermal hyperplasia	0	0	50 ** , ##	TPA	1.1 ± 1.5	17.9 ± 8.9	0.5 ± 0.7
Squamous papilloma	0	0	100 ** , ##				
Keratoacanthoma	0	0	35 ** , ##				

**: P<0.01 (Fisher), vs. acetone

##: P<0.01 (Fisher), vs. ethanol

**: P<0.01 (Wilcoxon), vs. acetone

##: P<0.01 (Wilcoxon), vs. ethanol

Tumor incidence (%)

Average number of tumors

Results

No tumors were observed in the group treated with acetone, the vehicle control, or ethanol. In the group administered TPA, the positive control article, tumors were confirmed from 6 weeks after administration, and **tumors were confirmed in all cases** by 18 weeks after administration. Histopathological examination showed that the masses on the dorsum skin were mainly papillomas, with **the incidence of 100%**. The above results confirmed that this study can be used to predict whether or not the test article is carcinogenic.