예시 1

국가·국제기구 평가보고서를 통한 시험항목의 자료제출 생략사유 및 증명자료

대상물질 : Linalool(CAS No.78-70-6)

시험항목 : 발암성

등록제출자료 생략의 사유

(출처명) 본 생략사유 및 증명자료는 OECD SIDS 초기평가 보고서(SIAR: SIDS Initial Assessment Report For 14th SIAM,2002) 결과를 참고하였습니다.

(주요 종말점 및 결과값과 주요영향) Linalool(CAS No.78-70-6)의 발암성 시험은 마우스(용량군당 암수 15마리씩)를 이용한 시험에서 복강주사(8주간 주3회)로 저용량(0.6 g/kw bw)과 고용량(3 g/kw bw)에서 일부 시험동물에게 폐종양이 발견되었지만 이러한 발생률은 대조군과 유의미한 차이가 없었고, 랫드(암컷 50마리)를 이용한 시험에서 경구투여(20주간 feed)로 1% 용량에서 유방종양 발생률과 잠복기는 대조군과 유의미한 차이가 없다고 기술되어 있습니다. 또한 이러한 시험결과를 근거로 Linalool(CAS No.78-70-6)은 발암성이 아닌 것으로 판단한다고 기술되어 있습니다.

(GHS 분류) 해당결과는 UN GHS 및 「화학물질의 분류 및 표시 등에 관한 규정(국립환경과학원고시 제2021-18호)」에 따라 발암성 분류기준에 해당되지 않는다고 판단할 수 있습니다.

(생략 시험항목) 이에 화학물질의 등록 및 평가 등에 관한 법률 시행령 제13조 제6호의2에 따라 Linalool(CAS No.78-70-6)의 발암성 자료를 생략하고자 합니다.

증명자료

생략사유의 증명자료로 아래와 같이 해당자료의 국문요약을 참고로 제시합니다.

<표> 최기형성 시험결과(요약)

출처: SIDS Initial Assessment Report for 14th SIAM [2002], 127~130쪽

No.	자료개요 및 시험방법	시험결과
1	- **자료의 성격:** 주요자료, 요약서 - **신뢰도(결과도출방법 등):** 신뢰도 2 (valid with restrictions) - **근거(인용):** OECD SIAR 발암성 평가 자료 인용	- **종말점 및 결과값:** negative - **시험용량별 영향:** • 총 용량 3 g/kg bw, 수컷, 9마리 생존, 종양 포함 2마리

No.	자료개요 및 시험방법	시험결과
	- **시험방법:** 국가·국제기구 등의 시험지침 기술되지 않음 • 예비독성테스트로 MTD(Maximally Tolerated single Dose) 결정 후 시험 - **노출방법:** • 노출기간 : 8주 • 노출빈도 : 주 3회 • 노출경로 : 복강주사 - **GLP 준수여부:** GLP 미준수 - **시험물질 정보:** Linalool(순도 미기재) - **시험종 정보:** mouse (A/He mouse), 각각 15마리씩 4개의 그룹, 고용량과 저용량에서 암컷,수컷 각각 15마리 - **시험용량:** • 3 g/kg bw (고용량) • 0.60 g/kg bw (저용량)	• 총 용량 3 g/kg bw, 암컷, 11마리 생존, 종양 포함 3마리 • 총 용량 0.6 g/kg bw, 수컷, 11마리 생존, 종양 포함 1마리 • 총 용량 0.6 g/kg bw, 암컷, 9마리 생존, 종양 포함 1마리 - **주요영향:** 폐 종양 발생 발견 이러한 발생률은 대조군과 통계적으로 다르지 않음 , P > 0.05
2	- **자료의 성격:** 보조자료, 요약서 - **신뢰도(결과도출방법 등):** 신뢰도 2 (valid with restrictions) - **근거(인용):** OECD SIAR 발암성 평가 자료 인용 - **시험방법:** 국가·국제기구 등의 시험지침 기술되지 않음 - **노출방법:** • 노출기간 : 20 주 • 노출경로 : oral feed - **GLP 준수여부:** 알 수 없음 - **시험물질 정보:** Linalool(순도 미기재) - **시험종 정보:** 랫드(rat,Sprague-Dawley), 암컷 50마리 - **시험용량:** 1% w/w in powdered Wayne Lab Blox chow	- **종말점 및 결과값:** 시험그룹의 유방 종양 발생률이 낮고, 잠복기가 길었지만 두 효과 모두 통계적으로 유의하지 않음. - **주요영향:** • 시험그룹의 종양 잠복기가 대조군인 56일에 비하여 84일 이었음. P=0.08로 통계적으로 유의하지 않음 • 시험그룹은 총 96개의 종양 (동물당 1.9개) , 대조군은 총 119개의 종양(동물당 2.3개). P>0.1 통계적으로 유의하지 않음

[별첨(원문 페이지 발췌)]

GH시험결과 표(또는 내용)

5.7 Carcinogenicity

Species:	mouse Sex: male/female
Strain:	other: A/He mouse
Route of administration:	i.p.
Exposure period:	8 weeks
Frequency of treatment:	3 times weekly
Post exposure period:	16 weeks
Doses:	total dose = 3 g/kg bw for the high-dose group and 0.60 g/kg bw for the low-dose group
Result:	negative
Control Group:	other: yes, four concurrent control groups, one untreated negative control (50 m/50 f), one vehicle negative control (80 m/80 f) and two urethan-treated positive controls with different dose levels (10 mg: 20 m/20 f; 20 mg: 20 m/20 f)
Year:	1973
GLP:	no

Method:

Animals:
Male and female A/He mice were bought from the Institute for Cancer Research, Philadelphia, of from the US National Cancer Insitute. The 6- to 8-week old animals weighed an average of 18-20 g. They were randomly distributed among experimental and control groups. Groups of 5 were housed in plastic boxes. Commercial grade sawdust chips were used for bedding. Purina laboratory chow and water were available ad libitum. Hygienic conditions were maintained by twice-weekly changes of the animal cages and water bottles and weekly disinfection of animal quarters. The water bottles were routinely sterilised.
For tests with linalool, 4 groups of 15 animals each were used, one group each of 15 males and 15 females for the high and for the low dose.
Chemicals:
All chemicals were stored in the dark and prepared for injection in separate rooms at a distance from the animals.
Administration:
In a preliminary toxicology test, the maximally tolerated single dose (MTD) for each test substance was determined by injecting intraperitoneally serial two-fold dilutions of chemicals into groups of 5 mice. The MTD was defined as that maximum single dose that all 5 mice tolerated after receiving 6 i.p. injections over a 2-week period. For evidence of delayed toxicity, animals receiving 6 doses of

	the MTD were held for another 1-2 months before experimental groups were initiated. For linalool the MTD was determined to be 125 mg/kg bw. For the main carcinogenicity test series with food additives, including linalool, 2 dose levels were used, the MTD and a 1:5 dilution of the MTD. All injections of linalool were administered as 0.1 ml/dose of solutions in tricaprylin, with the dose adjusted to the body weight of the mice. Each chemical was injected i.p. 3 times per week for 8 weeks, totalling 24 doses. Duration: The experiments were terminated 24 weeks after the first injection. Examination and statistics: Treated and control animals were killed by cervical dislocation and dissected. The lungs were removed and fixed in Tellyesniczky's fluid. 3-4 days after fixation, the milky white nodules on the lung were counted and some were taken for histological examination. The lungs were also examined for the rpesence of other abormalities, eg inflammatory reactions and adenomatosis. Liver, kidney, spleen, thymus, intestine and salivary and endocrine glands were examined at autopsy for the presence of abnormalities. Suspicious tissues were examined as to type and catalogued with respect to incidence. Tumour incidences in treated and appropriate vehicle control animals were compared by the standard chi-square test to determine whether a compound was positive, ie producing significantly more tumours.
Result:	In the linalool treatment groups of 15 animals each the following incidences of pulmonary tumours was found: 1) total dose 3 g/kg bw, males, 9 survivors, 2 with 1 tumour; 2) total dose 3 g/kg bw, females, 11 surv., 3 with 1 tumour; 3) total dose 0.6 g/kg bw, males, 11 surv., 1 with 1 tumour; 4) total dose 0.6 g/kg bw, females, 9 surv., 1 with 1 tumour. These incidences were not statistically different from vehicle controls, P > 0.05
Test substance:	as prescribed by 1.1 - 1.4: Linalool, Lot no. 1777162, from Givaudan. Test substance was stored at 4 °C.
Reliability:	(2) valid with restrictions
Flag:	Critical study for SIDS endpoint
20-JUL-2001	(138)

Species:	rat	Sex: female
Strain:	Sprague-Dawley	
Route of administration:	oral feed	
Exposure period:	20 weeks	
Doses:	1% w/w in powdered Wayne Lab Blox chow	
Control Group:	yes, concurrent no treatment	

Year:	1989
GLP:	no data
Test substance:	as prescribed by 1.1 - 1.4

Method: 6-week-old female rats were randomised to experimental (n = 50 rats) and control groups (n = 51 rats) and fed experimental (1% test substance, linalool) and control diets for two weeks. Then, mammary tumours were induced with 7,12-dimethylbenz[a]anthracene (DMBA) in the 55-day-old experimental and control rats with a single gastric intubation of 65 mg DMBA/kg bw in 0.5 ml sesame oil. Rats were further fed control or experimental diets; the latter were extensively mixed with test compound, prepared bi-weekly and stored in sealed containers at -20 °C. Chow was replaced in the feed cups 3 times per week. Starting 5 weeks post-intubation with DMBA, the rats were weighed and palpated for mammary tumours at weekly intervals. All tumours were fixed and processed for histopathology. More than 95% of the tumours were mammary carcinomas.
The effectiveness of the various monoterpenoids, including linalool, was evaluated on the basis of the time to appearance of the first tumour (tumour latency). Comparison of latencies between treated and control groups was made by one-sided log-rank test. Total tumour numbers per treatment group were also registered and compared on the basisa of a chi-square test adjusted for total number of days at risk.

Result: The linalool treatment group had a median tumour latency of 84 days compared to 56 days for controls; at P = 0.08 this difference was not statistically significant. The linalool treatment group had 96 tumours overall (1.9 per animal) while the control group had 119 tumours (2.3 per animal); at P > 0.1, this difference was not statistically significant.

Conclusion: The linalool group had both a lower incidence of mammary tumours and a longer median latency, however, both effects were not statistically significant.

Reliability: (2) valid with restrictions

04-DEC-2001 (125)

시험결과의 결론

carcinogenicity test from 1960. In contrast, it was not tumour-promoting, but rather tumour-inhibiting or tumour-delaying, in a later oral feed co-carcinogenicity study.

In conclusion, linalool has a moderate to low acute, subchronic and reproductive toxicity towards mammals. It is a moderate irritant but has a low sensitising potential. Further, it is not mutagenic nor carcinogenic. While the entero-hepato-biliary recirculation in metabolism may prolong the load on the liver, linalool is still excreted relatively rapidly by pulmonary and urinary pathway and there is no tendency for bioaccumulation. The overall toxicity of linalool is low.