예시 1

국가·국제기구 평가보고서를 통한 시험항목의 자료제출 생략사유 및 증명자료

대상물질 : Vanillin(cas no. 121-33-5)

시험항목 : 급성경구독성

등록제출자료 생략의 사유

(출처명) 본 생략사유 및 증명자료는 OECD SIDS 초기평가 보고서(SIAR: SIDS Initial Assessment Report for SIAM, 1996) 결과를 참고하였습니다.

(주요 종말점 및 결과값과 주요영향) Vanillin(cas no. 121-33-5)의 주요 급성경구독성 LD_{50} 값은 3,925 mg/kg(랫드 암수; GLP), 3,978 mg/kg(랫드 암수; GLP), 4,200 mg/kg bw(랫드 암수), 3,300 mg/kg bw(랫드)으로 기술되어 있습니다.

(GHS 분류) 해당결과는 UN GHS 및 「화학물질의 분류 및 표시 등에 관한 규정(국립환경과학원고시 제2021-18호)」에 따라 급성경구독성 LD_{50} 값이 > 2,000 mg/kg인 분류 기준에 해당되지 않으므로 ‘분류되지 않음’으로 유해성을 판단할 수 있습니다.

(생략 시험항목) 이에 화학물질의 등록 및 평가 등에 관한 법률 시행령 제13조 제6호의2에 따라 Vanillin(cas no. 121-33-5)의 급성경구독성 자료를 생략하고자 합니다.

증명자료

생략사유의 증명자료로 아래와 같이 해당자료의 국문요약을 참고로 제시합니다.

<표> 급성경구독성 시험결과(요약)

출처: SIDS Initial Assessment Report for SIAM(1996), 10쪽, 23쪽, 59~61쪽.

No.	자료개요 및 시험방법	시험결과
1	- **자료의 성격:** 주요자료, 요약서 - **신뢰도:** 신뢰도 기준 및 근거가 기술되지 않음 - **근거(인용):** OECD SIAR 급성경구독성 평가 자료 - **시험방법:** OECD TG 401 (1987) and Directive 84/449/EEC, B.1 (1984) - **노출방법:** 경구(위관 삽입) - **GLP 준수여부:** GLP 준수 - **시험물질 정보:** Vanillin(순도: 99.9%) - **시험종 정보:** Rat(Sprague Dawley), 암수 총 40마	- **종말점 및 결과값:** • LD_{50} = 3925 mg/kg (rat) • LD_{50} = 3978 mg/kg (rat) - **주요영향:** 체중증가는 대조군과 유사하였으며, 사망한 동물에서 일부 폐 울혈을 제외하고는 육안으로 보이는 증상은 관찰되지 않음

No.	자료개요 및 시험방법	시험결과
	리(용량군 당 암컷 5마리, 수컷 5마리) - **시험용량:** 2000, 2510, 3160, 3980 mg/kg	
2	- **자료의 성격:** 주요자료, 요약서 - **신뢰도:** 신뢰도 기준 및 근거가 기술되지 않음 - **근거(인용):** OECD SIAR 급성경구독성 평가 자료 - **시험방법:** OECD TG 401 and Directive 79/831/EEC Annex V, B1. - **노출방법:** 경구(위관 삽입) - **GLP 준수여부:** 알 수 없음 - **시험물질 정보:** Vanillin(순도: 99.8%) - **시험종 정보:** Rat(Sprague Dawley), 암수 총 40마리(용량군 당 암컷 5마리, 수컷 5마리) - **시험용량:** 2500, 3200, 4000, 5000 mg/kg	- **종말점 및 결과값** • LD_{50} = 4200 mg/kg bw (rat, males and females) • LD_{50} = 3800 mg/kg bw (rat, males only) • LD_{50} = 4600 mg/kg bw (rat, females only)
3	- **자료의 성격:** 주요자료, 요약서 - **신뢰도:** 신뢰도 기준 및 근거가 기술되지 않음 - **근거(인용):** OECD SIAR 급성경구독성 평가 자료 - **시험방법:** OECD TG 401과 유사한 방법 - **노출방법:** 경구(위관 삽입, 10% 옥수수기름 현탁액으로 투여) - **GLP 준수여부:** GLP 미준수 - **시험물질 정보:** Vanillin(순도 미기재) - **시험종 정보:** Rat(Sprague Dawley), 총 15마리(용량군 당 5마리) - **시험용량:** 2510, 3160, 3980 mg/kg	- **종말점 및 결과값:** LD_{50} = 3,300 mg/kg (rat) - **주요영향:** 사망한 동물에서 폐 및 간 충혈과 위장 염증이 관찰됨
4	- **자료의 성격:** 보조자료, 요약서 - **신뢰도:** 신뢰도 기준 및 근거가 기술되지 않음 - **근거(인용):** OECD SIAR 급성경구독성 평가 자료 - **시험방법:** Litchfield & Wilcoxon (1949) - **노출방법:** 경구(propyleneglycol에서 20% 용액으로 희석하여 투여), 관찰기간 2주 - **GLP 준수여부:** GLP 미준수 - **시험물질 정보:** Vanillin(순도 미기재) - **시험종 정보:** Rat(Osborne Mendel), 암수 총 10마리 - **시험용량:** 기술되지 않음	- **종말점 및 결과값:** LD_{50} = 1,580 mg/kg (rat) - **주요영향:** 노출 직후 혼수상태에 이르렀으며, 4시간에서 4일 사이 사망
5	- **자료의 성격:** 보조자료, 요약서 - **신뢰도:** 신뢰도 기준 및 근거가 기술되지 않음 - **근거(인용):** OECD SIAR 급성경구독성 평가 자료 - **시험방법:** 국가·국제기구 등의 시험지침 기술되지 않음 - **노출방법:** 경구(옥수수기름 현탁액으로 투여)	- **종말점 및 결과값:** LD_{50} = 2,000 mg/kg (rat)

No.	자료개요 및 시험방법	시험결과
	- **GLP 준수여부:** GLP 미준수 - **시험물질 정보:** Vanillin(순도 미기재) - **시험종 정보:** Rat - **시험용량:** 기술되지 않음	
6	- **자료의 성격:** 보조자료, 요약서 - **신뢰도:** 신뢰도 기준 및 근거가 기술되지 않음 - **근거(인용):** OECD SIAR 급성경구독성 평가 자료 - **시험방법:** Thompson moving average method - **노출방법:** 경구(0.5% methyl cellulose 수용액에 20% 또는 40% 현탁액으로 투여), 관찰기간 7일 - **GLP 준수여부:** GLP 미준수 - **시험물질 정보:** Vanillin(순도 미기재) - **시험종 정보:** Rat(albino), 수컷 총 25마리(용량군 당 수컷 5마리) - **시험용량:** 2150, 3160, 4640, 6810, 10,000 mg/kg	- **종말점 및 결과값:** LD_{50} = 3,830 mg/kg (rat) - **주요영향:** 사망한 동물에서 폐 출혈, 위장자극, 신장 및 부신 울혈이 관찰됨
7	- **자료의 성격:** 보조자료, 요약서 - **신뢰도:** 신뢰도 기준 및 근거가 기술되지 않음 - **근거(인용):** OECD SIAR 급성경구독성 평가 자료 - **시험방법:** Litchfield & Wilcoxon (1949) - **노출방법:** 경구(propyleneglycol에서 20% 용액으로 희석하여 투여), 관찰기간 2주 - **GLP 준수여부:** GLP 미준수 - **시험물질 정보:** Vanillin(순도 미기재) - **시험종 정보:** Guinea Pig, 암수 총 10마리 - **시험용량:** 기술되지 않음	- **종말점 및 결과값:** LD_{50} = 1,400 mg/kg (Guinea Pig) - **주요영향:** 1시간 이내 우울 증상을 보였으며, 1일에서 3일사이 사망

[별첨(원문 페이지 발췌)]

시험결과의 결론

4.2 Effects on Human Health

a) Mode of action of the chemical, toxicokinetics and metabolism

Metabolism studies in rats have shown that vanillin is metabolised to a number of urinary products, primarily vanillic acid, in both free and conjugated forms. Only minor amounts of unmetabolised vanillin is excreted. One person who ingested 100 mg vanillin excreted 96 mg as vanillic acid (94% of the dose) in the next 24 hour period.

b) Acute toxicity

The acute toxicity studies conducted with vanillin are summarised in the following table.

Acute toxicity studies with vanillin

Species, strain	No	Administration	Endpoint	Value (mg/kg)
Rat, Sprague Dawley (GLP)	40	Oral, gavage	LD_{50}	3925-3976
Rat, Sprague Dawley	40	Oral, gavage	LD_{50}	4200
Rat, Sprague Dawley	15	Oral, gavage	LD_{50}	3300
Rat, Osborn Mendel	10	Oral	LD_{50}	1580
Rat	-	Oral	-	2000
Rat, albino	25	Oral	LD_{50}	3830
Guinea Pig	10	Oral	LD_{50}	1400
Rat, Sprague Dawley (GLP)	10	Dermal, paste	LD_0	>2000
Rabbit	3	Dermal	LD_{50}	>5010
Rat, Sprague Dawley	-	Intraperitonal	LD_{50}	1160
Mouse	-	Intraperitonal	LD_{50}	780
Mouse	-	Intraperitonal	LD_{50}	475
Guinea Pig	-	Intraperitonal	LD_{50}	1190
Rat, albino	50	Subcutaneous	LD_{50}	2600
Dog	-	Intravenously	LDL_0	1320

The acute toxicity (LD_{50}) of orally administered vanillin to rats seems, when taking into account the more recent and properly conducted studies, to be in the range of 3500 - 4000 mg/kg. When administered intraperitonally, intravenously or subcutaneously, the toxicity seems somewhat higher, while little toxicity has been seen after dermal application. No data are available on the acute toxicity of inhaled vanillin.

c) Repeated dose toxicity

GHS 분류결과

1.6 LABELLING AND CLASSIFICATION

A. Labelling

(a)	
Type:	Directive 67/548/EEC
Specific limits:	
Symbols:	
Nota:	
R-phrases:	
S-phrases:	
Text of S-phrases:	
Remarks:	No labelling required (no dangerous properties)
(b)	
Type:	Other: Directive 88/388/EEC.
Remarks:	Requirements: - Name of producer - "Aroma" or "Vanillin" - For food - Nature identical flavouring - Identification of the lot - Weight/Volume This is valid for Vanillin sold for manufacturing of food products.

B. Classification

Type:	Directive 67/548/EEC
Category of danger:	
R-phrases:	
Remarks:	No classification required (no dangerous properties)

시험결과 내용

5. TOXICITY

5.1 ACUTE TOXICITY

5.1.1 ACUTE ORAL TOXICITY

(a)

Type:	LD_0 ( ); LD_{100} ( ); LD_{50} (x); LDL_0 ( ); Other ( )
Species/strain:	Rat, Sprague Dawley
Value:	3925[1] and 3978[2] mg/kg
Method:	OECD TG 401 (1987) and Directive 84/449/EEC, B.1 (1984) "Acute toxicity (oral)"
GLP:	Yes (x) No ( ) ? ( )
Test substance:	As prescribed by 1.1-1.2. (Lot no. 90-24-701 from Rhône-Poulenc, France) Purity: 99.9%
Remarks:	Single ingastric intubation as a suspension in aqueous solution of 1% (w/v) carboxymethylcellulose at the dose levels 2000, 2510, 3160 and 3980 mg/kg. 5 males and 5 females per group. (1) Bliss' method: LD_{50} = 3978 mg/kg (2484-6368) (2) Litchfield & Wilcoxon's method: LD_{50} = 3925 mg/kg (2834-5435) Body weight gained similar to control; no macroscopical anomali observed, except some congestive lungs in dead animals.
Reference:	Lheritier, 1992.

(b)

Type:	LD_0 ( ); LD_{100} ( ); LD_{50} (x); LDL_0 ( ); Other ( )
Species/strain:	Rat, Sprague Dawley
Value:	4200[1], 3800[2] and 4600[3] mg/kg bw
Method:	OECD TG 401 and Directive 79/831/EEC Annex V, B1.
GLP:	Yes ( ) No ( ) ? (x)
Test substance:	As prescribed by 1.1-1.2. (Batch no. 132 dated 18.09.86, from EuroVanillin KS, Norway) Purity: 99.8%
Remarks:	Dose levels: 2500, 3200, 4000 and 5000 mg/kg. 5 males and 5 females per group. 95% confidence limits in parenthesis: (1) Males and females combined: LD_{50} = 4200 mg/kg (3600-5400) (2) Males only: LD_{50}= 3800 mg/kg (2900-5000) (3) Females only: LD_{50} = 4600 mg/kg (3700-6900)
Reference:	Gardner, 1987.

(c)

Type:	LD_0 ( ); LD_{100} ( ); LD_{50} (x); LDL_0 ( ); Other ( )
Species/strain:	Rat, Sprague Dawley
Value:	3300 mg/kg
Method:	Similar to OECD TG 401.
GLP:	Yes ( ) No (x) ? ( )

시험결과 내용

Test substance:	Vanillin from Monsanto Chemical Company (USA)
Remarks:	Vanillin in suspension of 10% corn oil. 5 rats per group. Dose levels: 2510, 3160 and 3980 mg/kg. LD_{50}: 3300 mg/kg (3100-3530). At autopsy, lung and liver hypermia and gastrointestinal inflammation in dead animals. Viscera appeared normal in survivors.
Reference:	Younger Laboratories Inc., 1976.
(d)	
Type:	LD_0 ( ); LD_{100} ( ); LD_{50} (x); LDL_0 ( ); Other ( )
Species/strain:	Rat, Osborne Mendel
Value:	1580 mg/kg
Method:	Litchfield & Wilcoxon (1949)
GLP:	Yes ( ) No (x) ? ( )
Test substance:	Vanillin; commercially available material.
Remarks:	Vanillin was diluted in propyleneglycol to a 20% (w/v) solution. 10 young adult rats, evenly divided by sex. Were fasted approx. 18 hours prior to treatment. Observation period: 2 weeks. Coma soon after treatment. Death time: 4 hours to 4 days.
Reference:	Jenner et al. 1964.
(e)	
Type:	LD_0 ( ); LD_{100} ( ); LD_{50} (x); LDL_0 ( ); Other ( )
Species/strain:	Rat
Value:	2000 mg/kg
Method:	No data
GLP:	Yes ( ) No (x) ? ( )
Test substance:	Vanillin; no further data
Remarks:	Single doses of Vanillin as a suspension in corn oil. 95% confidence limits in parenthesis: LD_{50} = 2000 mg/kg (1600-2500).
Reference:	Hake et al, 1963.
(f)	
Type:	LD_0 ( ); LD_{100} ( ); LD_{50} (x); LDL_0 ( ); Other ( )
Species/strain:	Rat, albino
Value:	3830 mg/kg
Method:	Thompson moving average method.
GLP:	Yes ( ) No (x) ? ( )
Test substance:	Vanillin from Monsanto Chemical Company, USA.
Remarks:	Administration as a 20% or 40% suspension in 0,5% solution of methyl cellulose. 5 male rats per group. Dose levels: 2150, 3160, 4640, 6810 and 10,000 mg/kg. Observation period: 7 days. LD_{50} = 3830 mg/kg (2930-5000). Hemorragic lungs, irritation gastrointestinal, congested kidneys and adrenals in dead animals. No gross pathology in survivors.

시험결과 내용

Reference:	Hazleton Laboratory, 1955.
(g)	
Type:	LD_0 ( ); LD_{100} ( ); LD_{50} (x); LDL_0 ( ); Other ( )
Species/strain:	Guinea Pig
Value:	1400 mg/kg (1310-1500 mg/kg)
Method:	Litchfield & Wilcoxon (1949).
GLP:	Yes ( ) No (x) ? ( )
Test substance:	Vanillin; commercially available material.
Remarks:	Vanillin was diluted in propyleneglycol to a 20% (w/v) solution. 10 guinea pigs, evenly divided by sex. Were fasted approx. 18 hours prior to treatment. Observation period: 2 weeks. Depression within 1 hour. Death time: 1-3 days.
Reference:	Jenner et al, 1964.

5.1.2 ACUTE INHALATION TOXICITY

Type:	
Species/strain:	
Exposure time:	
Value:	No data
Method:	
GLP:	
Test substance:	
Remarks:	
Reference:	

5.1.3 ACUTE DERMAL TOXICITY

(a)	
Type:	LD_0 (x); LD_{100} ( ); LD_{50} ( ); LDL_0 ( ); Other ( )
Species/strain:	Rat, Sprague Dawley
Value:	>= 2000 mg/kg
Method:	OECD TG 402 (1987), Directive 84/449/EEC (1984), E.P.A. guideline no. 798.1100 (1985) and M.A.F.F. guideline no. 4200 (1985).
GLP:	Yes (x) No ( ) ? ( )
Test substance:	As prescribed by 1.1-1.2. (Lot no. 90-24-701 from Rhône-Poulenc, France) Purity: 99.9%
Remarks:	Limit test. 5 male and 5 female. Unique dose 2000 mg/kg. A paste of ca. 70% Vanillin in purified water was applied on the shaved skin (10% body area) for 24 hours using semi-occusive patch. Examination after 15 minutes, 1,2 and 4 hours and daily for 14 days. No mortality or pathological clinical sign. No cutaneous lesions. No macroscopic anomali at necropsy.

예시 2

국가·국제기구 평가보고서를 통한 시험항목의 자료제출 생략사유 및 증명자료

대상물질 : Morpholine(CAS No. 110-91-8)

시험항목 : 급성경구독성

등록제출자료 생략의 사유

(출처명) 본 생략사유 및 증명자료는 OECD SIDS 초기평가 보고서(SIAR: SIDS Initial Assessment Report for CoCAM 5) 및 SIDS Dossier 결과를 참고하였습니다.

(주요 종말점 및 결과값과 주요영향) Morpholine(CAS No. 110-91-8)의 급성경구독성 LD_{50} 값은 약 1,900 mg/kg bw(랫드 암수), 1,680mg/kg bw(랫드 수컷), 1,050mg/kg bw(랫드 암컷)으로 기술되어 있습니다.

(GHS 분류) 해당결과는 UN GHS 및 「화학물질의 분류 및 표시 등에 관한 규정(국립환경과학원고시 제2021-18호)」에 따라 급성경구독성 LD_{50} 값이 > 300 mg/kg, ≤2,000 mg/kg인 '구분 4'에 해당하는 유해성을 판단할 수 있습니다.

(생략 시험항목) 이에 화학물질의 등록 및 평가 등에 관한 법률 시행령 제13조 제6호의2에 따라 Morpholine(CAS No. 110-91-8)의 급성경구독성 자료를 생략하고자 합니다.

증명자료

생략사유의 증명자료로 아래와 같이 해당자료의 국문요약을 참고로 제시합니다.

<표> 급성경구독성 시험결과(요약)

출처: SIDS Initial Assessment Report for CoCAM 5(2013), 19~20쪽, SIDS Dossier, 220~228쪽

No.	자료개요 및 시험방법	시험결과
1	- **자료의 성격:** 주요자료, 요약서 - **신뢰도:** 신뢰도 2(reliable with restrictions) - **근거(인용):** OECD SIAR 급성경구독성 평가 자료 - **시험방법:** OECD TG 401과 유사한 시험방법 - **노출방법:** 경구(위관 삽입), 관찰기간 14일 - **GLP 준수여부:** GLP 미준수 - **시험물질 정보:** Tetrahydro-2H-1,4-oxazine; Morpholine (순도: 99.2%) - **시험종 정보:** rat(Sprague-Dawley), 1600, 2000, 3	- **종말점 및 결과값:** LD_{50} = ca. 1,900 mg/kg bw (rat) - **시험용량별 영향:** • 3200, 2500mg/kg bw에서 쪼그리고 앉은 자세, 주름진 털, 복부 자세, 얕고 불규칙한 호흡, 눈감음이 관찰됨 • 2000, 1600mg/kg bw에서 빠른 호흡, 쪼그리고 앉은 자세, 코에서 붉은 딱지, 높은 걸음걸이가 관찰됨

No.	자료개요 및 시험방법	시험결과
	200 mg/kg 용량군에서 암수 5마리 및 2500 mg/kg 용량군에서 10마리 - **시험용량**: 1600, 2000, 2500, 3200mg/kg bw	- **주요영향**: 죽은 동물 중 4마리에서 설사의 흔적, 1마리에서 장내 출혈이 육안으로 확인됨
2	- **자료의 성격**: 주요자료, 요약서 - **신뢰도**: 신뢰도 2(reliable with restrictions) - **근거(인용)**: OECD SIAR 급성경구독성 평가 자료 - **시험방법**: OECD TG 401과 유사한 시험방법 - **노출방법**: 경구(위관 삽입), 관찰기간 3일 - **GLP 준수여부**: 알 수 없음 - **시험물질 정보**: Tetrahydro-2H-1,4-oxazine; Morpholine (순도: 99.2%) - **시험종 정보**: rat(Sprague-Dawley), 용량군 당 수컷 4마리 - **시험용량**: 250, 500, 1000, 2000, 4000 mg/kg bw	- **종말점 및 결과값**: LD_{50} = 1,680mg/kg bw (rat) - **시험용량별 영향**: 250, 500, 1000 mg/kg bw에서 사망개체가 관찰되지 않았음. 2000mg/kg bw에서 3마리, 4000mg/kg bw에서 4마리 사망개체 관찰됨
3	- **자료의 성격**: 보조자료, 요약서 - **신뢰도**: 신뢰도 2(reliable with restrictions) - **근거(인용)**: OECD SIAR 급성경구독성 평가 자료 - **시험방법**: OECD TG 401과 유사한 시험방법 - **노출방법**: 경구(위관 삽입), 관찰기간 14일 - **GLP 준수여부**: GLP 미준수 - **시험물질 정보**: Tetrahydro-2H-1,4-oxazine; Morpholine(순도 미기재) - **시험종 정보**: rat(Carworth-Wistar), 용량군 당 암컷 5마리 - **시험용량**: 기술되지 않음	- **종말점 및 결과값**: • LD_{50} = 1,050mg/kg bw (rat)
4	- **자료의 성격**: 보조자료, 요약서 - **신뢰도**: 신뢰도 2(reliable with restrictions) - **근거(인용)**: OECD SIAR 급성경구독성 평가 자료 - **시험방법**: OECD TG 401과 유사한 시험방법 - **노출방법**: 경구(위관 삽입) - **GLP 준수여부**: GLP 미준수 - **시험물질 정보**: Tetrahydro-2H-1,4-oxazine; Morpholine, (순도: 98% 이상) - **시험종 정보**: Guinea pig, 총 33마리 - **시험용량**: 0.1 ~ 10g/kg bw	- **종말점 및 결과값**: • MLD=900mg/kg bw (Guinea pig) - **시험용량별 영향**: • 사망개체는 900, 1000mg/kg bw에서 10마리 이상의 동물 중 절반 미만으로 관찰됨 • 1600mg/kg bw에서 증상이 관찰되지 않았음

[별첨(원문 페이지 발췌)]

시험결과의 결론

Conclusion

Acute inhalation studies are available for morpholine, although discrete LC_{50} values were not determined. There was no mortality in rats exposed to nominal concentrations of 24 mg/L for 4 hours (similar to OECD TG 403). There were signs of irritation, but no effects on body weight and no findings at gross necropsy. There was 100% mortality in rats exposed to vapour concentrations of 21.14 mg/L (nominal) for 5.5 hours or 4.6-5.4 mg/L (measured) for 6 hours; 33% mortality was found in rats exposed to 28.8 mg/L (nominal) for 3 hours (similar to OECD TG 403). Clinical signs and findings at gross necropsy were consistent with generally severe local effects of eye and respiratory irritation, respiratory distress and lung damage. A dermal LD_{50} value (rabbit) of 500 mg/kg bw was determined following a 24-hour occluded exposure (similar to OECD TG 402); clinical signs were not reported in this study. Oral LD_{50} values were 1050-1900 mg/kg bw in rats (all studies similar to OECD TG 401). Clinical signs reported include breathing abnormalities, oral-nasal wetness and/or staining, effects on gait, postural abnormalities, and eye closure. Site of contact effects (irritation/corrosion) in the gastrointestinal tract were the only findings noted at gross necropsy. Based on the oral toxicity studies, females may be more sensitive than males.

GHS 분류결과

Health hazards

	Hazard category	Hazard statement	Reason for no classification
Acute toxicity - oral	Acute Tox. 4	H302: Harmful if swallowed.	

시험결과 내용

▪ *Oral*

(1) In a study similar to OECD TG 401, groups of male and female Sprague-Dawley rats were administered morpholine (99.2 % purity) by gavage in water (BASF AG, 1967). There were five animals/sex at 1600, 2000 and 3200 mg/kg bw and ten animals/sex at 2500 mg/kg bw. Animals were observed for mortality and clinical signs of toxicity for 14 days following dosing. All ten animals died at 3200 mg/kg bw; 4/10 males and all ten females died at 2500 mg/kg bw; 1/5 males and all females died at 1600 mg/kg bw; and 1/5 males and 1/5 females died at 2000 mg/kg bw. These data indicate females may be more sensitive than males to morpholine administered orally. At 3200 and 2500 mg/kg bw clinical signs included squatting posture, ruffled fur, abdominal position, shallow and irregular respiration, and closed eyes. After 24 hours, the surviving animals showed red crusted eyes and noses, and trembling gait with delayed motion of the hind limbs. At 1600 and 2000 mg/kg bw, clinical signs included fast respiration, squatting posture, red crusted noses, and exaggerated gait. There were no findings at gross necropsy for surviving animals. The oral LD_{50} for the combined sexes was 1900 mg/kg bw; the oral LD_{50} for females would be lower than this.

(2) In an acute oral toxicity study similar to OECD TG 401, male Sprague-Dawley rats (4/dose) were administered morpholine (99.2% purity) by gavage at doses of 250, 500, 1000, 2000, and 4000 mg/kg bw (Huntsman, 1981a). Animals were observed for 3 days following dosing. There were three and four deaths at doses of 2000 and 4000 mg/kg bw; there were no deaths at the three lower doses. There were no details provided regarding clinical signs, body weight or findings at gross necropsy. The oral LD_{50} was 1680 mg/kg bw.

(3) In a study similar to OECD TG 401, female Carworth-Wistar rats (5/dose) were administered morpholine (purity not reported) by gavage (in water, corn oil or 1 % Tergitol Penetrant 7) (Smyth *et al.*, 1954). A logarithmic series of dose levels were administered at a dose volume of 1 to 10 mL/rat, and animals were observed for 14 days following dosing. There were no details provided regarding mortalities, clinical signs, body weight or findings at gross necropsy. The oral LD_{50} was 1050 mg/kg bw.

(4) In an acute oral toxicity study, albino rats and guinea pigs were administered morpholine (≥98% purity) undiluted or in water by gavage at doses ranging from 100 to 10,000 mg/kg bw (Shea, 1939). The number of animals/group and sex was not specified. Animals were observed for mortality and clinical signs for 7 days following dosing. Mortality incidence was not reported; all deaths in rats occurred within 2-3 days of dosing. In both species, gastrointestinal bleeding and haemorrhaging of the stomach was observed. Clinical signs in guinea pigs included collapse, prostration, and diarrhea; details regarding clinical signs in rats or body weight in either species were not provided. The oral LD_{50} in rat was 1600 mg/kg bw; the minimum lethal dose in guinea pigs was 900 mg/kg bw.

Table 3. Summary of Acute Toxicity

Test species/sex	Result (LD_{50}/LC_{50})	Reference
Inhalation		
Rat/male and female	<21.14 mg/L (5.5 hr)	BASF AG, 1967
Rat/male and female	<4.6 – 5.4 mg/L (6 hr, measured concentration)	Huntsman, 1981b
Rat/not specified	>23.6 mg/L (4 hr)	ILO, 1972
Dermal		
▪ Rabbit/male	500 mg/kg bw	Smyth *et al.*, 1954
▪ Rabbit/not specified	>900 mg/kg bw	Shea, 1939
Oral		
▪ Rat/male and female	1900 mg/kg bw	BASF AG, 1967
▪ Rat/male	1680 mg/kg bw	Huntsman, 1981a
▪ Rat/female	1050 mg/kg bw	Smyth *et al.*, 1954
▪ Rat/unspecified	1600 mg/kg bw	Shea, 1939

시험결과 내용

Purpose flag	key study; robust study summary
Study result type	experimental result
Study period	1967-02-05
Reliability	2 (reliable with restrictions)
Rationale for reliability incl. deficiencies	Acceptable, well documented report which meets basic scientific principles; non-GLP.

Data source

Reference

Reference type	Author	Year	Title	Bibliographic source	Testing laboratory	Report no.	Owner company	Company study no.	Report date
study report	BASF AG	1967	Industrial hygiene orientating investigation.	unpublished data	BASF AG, Department of Toxicology	XVI/352	BASF SE		1967-02-05

Data access

data submitter is data owner

Materials and methods

Test type

standard acute method

Limit test

no

Test guideline

Qualifier	Guideline	Deviations
equivalent or similar to	OECD Guideline 401 (Acute Oral Toxicity)	no data

Principles of method if other than guideline

BASF-Test, see details in the section "Any other information on materials and methods incl. tables".

GLP compliance

no (study was performed prior to GLP)

Test materials

Identity of test material same as for substance defined in section 1 (if not read-across)

yes

Test material identity

Identifier	Identity
CAS number	110-91-8
EC number	203-815-1

Details on test material

- Name of test material: Morpholine (1, 4-Tetrahydrooxazin)- Physical state: liquid- Analytical purity: 99.2 %- Impurities: 0.2 to 0.3 % water, 0.1 % diethylene glycol, 0.4 % n-ethylmorpholine.

Test animals

Species

rat

Strain

Sprague-Dawley

Sex

male/female

Details on test animals and environmental conditions

TEST ANIMALS- Age at study initiation: young adult (based on body weight)- Weight at study initiation: 180 to 288 g (male), 156 - 226 g (female)

Administration / exposure

Route of administration

oral: gavage

Vehicle

water

Details on oral exposure

VEHICLE- Concentration in vehicle: 4 and 20 %.

시험결과 내용

Doses

1600, 2000, 2500 and 3200 mL/kg bw = 1600, 2000, 2500 and 3200 mg/kg bw (conversion in mg/kg bw is based on the density d=1.00 g/cm³)

No. of animals per sex per dose

5 animals (at 1600, 2000 and 3200 mg/kg bw)10 animals (at 2500 mg/kg bw)

Control animals

no data

Details on study design

- Duration of observation period following administration: 14 days- Frequency of observations: several times on the day of application and daily thereafter - Necropsy of survivors performed: yes- Other examinations performed: clinical signs, macroscopical examination

Statistics

Not indicated.

Any other information on materials and methods incl. tables

The study was conducted according to an internal BASF method which in principle is comparable to the OECD Guideline 401. A test group consisting of 5 animals was treated by single gavage application with an aqueous solution of the test substance. The animals were observed for mortality and for clinical symptoms of toxicity. At the end of the observation period of 14 days, the surviving animals were sacrificed for the purpose of necropsy; animals that died during the observation period also were subjected to necropsy. The LD50 value was estimated on the basis of the observed mortalities.

Results and discussions

Effect levels

Sex	Endpoint	Effect level	Based on	95% CL	Remarks
male/female	LD50	ca. 1900 mg/kg bw			Based on the mortality data, the oral LD50 for females would be lower.

Mortality

See details in the section "Any other information on results incl. tables".

Clinical signs

At 3200 and 2500 mg/kg bw: squatting posture, ruffled fur, abdominal position, shallow and irregular respiration, closed eyes. After 24 hours the surviving animals showed red crusted eyes and noses, and trembling gait with delayed motion of the hind limbs.2000 and 1600 mg/kg bw: accellerated respiration, squatting posture, red crusted noses, high stepping gait.

Body weight

No data

Gross pathology

Animals that died: 4x diarrhoea, 1x haemorrhagic enteritis.Sacrificed animals: no abnormalities.

Any other information on results incl. tables

Mortality:

Dose (mg/kg bw)	Gender	1 h	24 h	48 h	7 days	14 days
3200	male	0/5	5/5	5/5	5/5	-
3200	female	0/5	5/5	5/5	5/5	-
2500	male	0/10	4/10	4/10	4/10	4/10
2500	female	0/10	10/10	10/10	10/10	10/10
2000	male	0/5	0/5	1/5	1/5	-
2000	female	0/5	5/5	5/5	5/5	-
1600	male	0/5	1/5	1/5	1/5	-
1600	female	0/5	1/5	1/5	1/5	-

The test substance caused dose dependent toxicity after a single ingestion and local irritations to exposed tissues.

Applicant's summary and conclusion

Executive summary

In an acute oral toxicity study according to an internal BASF method (BASF AG, 1967), Sprague Dawley rats were given a single oral dose of Morpholine (99.2 %) diluted in water at 1600, 2000, 2500 or 3200 mg/kg bw. Animals were then observed for mortality and for clinical symptoms of toxicity for 14 days. All animals were subjected to necropsy. The oral LD50 was estimated as 1900 mg/kg bw.

This acute oral study is classified as acceptable. It satisfies the guideline requirement for an acute oral study according to OECD 401 in principle.

시험결과 내용

Water: ad libitum

Administration / exposure

Route of administration

oral: gavage

Vehicle

no data

Doses

250, 500, 1000, 2000, 4000 mg/kg bw

No. of animals per sex per dose

4 animals

Control animals

no

Details on study design

- Duration of observation period following administration: 3 days

Statistics

LD50 calculated according to the method described by Weil (1952).

Any other information on materials and methods incl. tables

The study was conducted according to a test method which in principle is comparable to the OECD Guideline 401 with some deviations. A test group consisting of 4 animals was treated by single gavage application with the test substance. The animals were observed for mortality and for clinical symptoms of toxicity. At the end of the observation period of 3 days, the LD50 value was estimated on the basis of the observed mortalities.

Results and discussions

Effect levels

Sex	Endpoint	Effect level	Based on	95% CL	Remarks
male	LD50	1680 mg/kg bw			

Mortality

Number of animals dying within 3 days:250, 500, 1000 mg/kg bw: 0/42000 mg/kg: 3/44000 mg/kg: 4/4

Clinical signs

No data

Body weight

No data

Gross pathology

No data

Applicant's summary and conclusion

Executive summary

In an acute oral toxicity study (Huntsman, 1981), male Sprague Dawley rats were given a single dose (oral gavage) of Morpholine at 250, 500, 1000, 2000, or 4000 mg/kg bw. Animals were then observed for 3 days. The oral LD50 was estimated as 1680 mg/kg bw.

This acute oral study is classified as acceptable supporting study.

Endpoint study record: Supporting. Smyth 1954. Acute toxicity: oral, rat

UUID IUC5-a948faaf-d39e-4059-8461-2c38cf7b6e31
Dossier UUID 0
Author Collette / Epona Associates, LLC / Willington / United States
Date 2013-07-07 20:53:25 EDT
Remarks

Administrative Data

EU: REACH

Purpose flag	supporting study; robust study summary		
Study result type	experimental result	**Study period**	1954
Reliability	2 (reliable with restrictions)		

시험결과 내용

Details on study design
- Duration of observation period following administration: 14 days

Statistics
The most probable LD50 was estimated by the methods of Thompson (1947) and Weil (1952).

Any other information on materials and methods incl. tables
Single dose oral toxicity for rats was estimated by intubation of dosages in a logarithmic series to five female rats.

Results and discussions
Effect levels

Sex	Endpoint	Effect level	Based on	95% CL	Remarks
female	LD50	1050 mg/kg bw			

Mortality
No detailed information provided

Clinical signs
No information provided

Body weight
No information provided

Gross pathology
No information provided

Applicant's summary and conclusion
Executive summary
In a single dose study (Smyth, 1954), acute oral toxicity of Morpholine was estimated by oral gavage in 5 female Carworth-Wistar rats per dose level using a logarithmic series of doses. Morpholine was diluted with a vehicle when necessary to bring the dose volume to 1 to 10 mL per rat. 14 days after dosing, mortality was considered as complete. Oral administration of Morpholine to female rats resulted in a LD50 value of 1050 mg/kg bw.

This study is classified as acceptable supporting study.

Endpoint study record: Supporting.Shea 1939. Acute toxicity: oral, rat
UUID IUC5-9ed66865-2433-42a7-a8cf-2f5ec477622d
Dossier UUID 0
Author Collette / Epona Associates, LLC / Willington / United States
Date 2014-07-09 10:53:28 EDT
Remarks

Administrative Data
EU: REACH

Purpose flag supporting study; robust study summary

Study result type experimental result **Study period** 1939

Reliability 2 (reliable with restrictions)

Rationale for reliability incl. deficiencies Acceptable publication which meet basic scientific principles; prior to GLP

Data source
Reference

Reference type	Author	Year	Title	Bibliographic source	Testing laboratory	Report no.	Owner company	Company study no.	Report date
publication	Shea TE Jr	1939	THE ACUTE AND SUB-ACUTE TOXICITY OF MORPHOLINE	J. Ind. Hyg. Toxicol. 21: 236-245					

Data access
data published

Materials and methods
Test type
standard acute method

시험결과 내용

Limit test
no

Test guideline

Qualifier	Guideline	Deviations
equivalent or similar to	OECD Guideline 401 (Acute Oral Toxicity)	no data

GLP compliance
no (prior to GLP)

Test materials

Identity of test material same as for substance defined in section 1 (if not read-across)
yes

Test material identity

Identifier	Identity
CAS number	110-91-8
EC number	203-815-1

Details on test material
- Name of test material: Morpholine- Analytical purity: not less than 98 %

Test animals

Species
rat

Strain
other: albino

Sex
no data

Details on test animals and environmental conditions
No information provided in the publication.

Administration / exposure

Route of administration
oral: gavage

Vehicle
water

Details on oral exposure
Morpholine was either administered undiluted or diluted with 4 parts of water.

Doses
0.1 - 10 g/kg bw

No. of animals per sex per dose
not quoted; 57 rats were used in total.

Control animals
no data

Details on study design
57 rats were used to determine the minimum lethal dose (MLD), i.e., the dosage killing 50 % of the animals receiving it within 1 week.

Statistics
No information on statistics provided.

Results and discussions

Effect levels

Sex	Endpoint	Effect level	Based on	95% CL	Remarks
no data	LD50	1600 mg/kg bw			

Mortality
All deaths occurred within 2 or 3 days of dosing.

Clinical signs
Gastrointestinal bleeding, haemorrhage of the stomach

시험결과 내용

Body weight

No data

Gross pathology

Animals dying at 1600 mg/kg bw showed no pathological symptoms.

Any other information on results incl. tables

For rats 1600 mg/kg bw was the minimum lethal dose.

Applicant's summary and conclusion

Executive summary

In this acute oral toxicity study (Shea, 1939), rats were fed with undiluted or diluted Morpholine (in water) at doses ranging from 0.1 to 10 g/kg bw. The most constant symptom at high dose levels was haemorrhage of the stomach. 57 rats were used to determine the minimum lethal dose, i.e., the dosage killing 50 % of the animals receiving it within 1 week. All deaths in this study occurred within 2 or 3 days of dosing. The LD50 was 1600 mg/kg bw.

This study is classified as acceptable supporting study.

Endpoint study record: Supporting.Shea 1939. Acute toxicity: oral, guinea pig

UUID IUC5-1d04624c-c39d-4856-b7e8-ba37590b7147
Dossier UUID 0
Author Collette / Epona Associates, LLC / Willington / United States
Date 2014-07-09 10:53:49 EDT
Remarks

Administrative Data

EU: REACH

Purpose flag	supporting study; robust study summary		
Study result type	experimental result	**Study period**	1939
Reliability	2 (reliable with restrictions)		
Rationale for reliability incl. deficiencies	Acceptable publication which meet basic scientific principles; prior to GLP; reports only a minimum lethal dose, but not an LD50.		

Data source

Reference

Reference type	Author	Year	Title	Bibliographic source	Testing laboratory	Report no.	Owner company	Company study no.	Report date
publication	Shea TE Jr	1939	THE ACUTE AND SUB-ACUTE TOXICITY OF MORPHOLINE.	J. Ind. Hyg. Toxicol. 21: 236-245.					

Data access

data published

Materials and methods

Test type

standard acute method

Limit test

no

Test guideline

Qualifier	Guideline	Deviations
equivalent or similar to	OECD Guideline 401 (Acute Oral Toxicity)	no data

GLP compliance

no (prior to GLP)

Test materials

Identity of test material same as for substance defined in section 1 (if not read-across)

yes

본 자료는 ”화학물질등록평가법 시행령 제13조 및 같은법 시행규칙 제5조”에 따라 제출이 필요한 생략사유 및 증명자료의 예시로 추가검토·보완을 통해 수정·변경될 수 있으며 단순 참고자료로 활용하시기 바랍니다.

시험결과 내용

Test material identity

Identifier	Identity
CAS number	110-91-8
EC number	203-815-1

Details on test material

- Name of test material: Morpholine- Analytical purity: not less than 98 %

Test animals

Species

guinea pig

Strain

no data

Sex

no data

Details on test animals and environmental conditions

No data provided in the publication.

Administration / exposure

Route of administration

oral: gavage

Vehicle

water

Details on oral exposure

Morpholine was either administered undiluted or diluted with 4 parts of water.

Doses

0.1 - 10 g/kg bw

No. of animals per sex per dose

not quoted; 33 guinea pigs were used in total.

Control animals

no data

Details on study design

33 guinea pigs were used to determine the minimum lethal dose (MLD), i.e., the dosage killing 50 % of the animals receiving it within 1 week.

Statistics

No information on statistics provided.

Results and discussions

Effect levels

Sex	Endpoint	Effect level	Based on	95% CL	Remarks
no data	other: minimum lethal dose	900 mg/kg bw			

Mortality

Both 900 and 1000 mg/kg bw killed less than half of 10 or more animals receiving that amount.

Clinical signs

Complete collapse, prostration, diarrhoea and haemorrhage into the stomach were noted.

Body weight

No data

Gross pathology

No data

Any other information on results incl. tables

For guinea pigs, 900 mg/kg bw was the minimum lethal dose.

Applicant's summary and conclusion

Executive summary

In an acute oral toxicity study (Shea, 1939), guinea pigs were fed with undiluted or diluted Morpholine (in water, 20%) at doses ranging from 0.1 - 10 g/kg bw. Complete collapse and prostration, diarrhoea and haemorrhage into the stomach were observed among the majority of those animals dying from the effects of Morpholine. 33 guinea pigs were used, and both 900 and 1000