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DOSSIER TOXICOLOGIQUE

Exemplaire N°1

« Les renseignements contenus dans ce document sont basés sur l'état actuel de connaissance, à la date de mise à jour. Ils sont donnés de bonne foi.Il appartient à l'utilisateur, sous sa seule responsabilité, de s'assurer des conditions et possibilités d'utilisation du produit, au regard des dispositions législatives et réglementaires en vigueur. Notre responsabilité ne saurait être engagée en cas d'utilisation anormale du produit. »

TABLE DES MATIERES

CD ROM

I-DEFINITION DE LA TOXICITE

1-SUBSTANCES ET PREPARATIONS :

Selon l'article 2, premier paragraphe, alinea a et b de la directive 1999/45/CE du Parlement Européen et du Conseil du 31 Mai 1999, les substances et les préparations sont définies de la sorte:

-« substances » : les éléments chimiques et leurs composés à l'état naturel ou tels qu'obtenus par tout procédé de production, y compris tout additif nécessaire pour préserver la stabilité du produit et toute impureté dérivant du procédé, mais à l'exclusion de tout solvant qui peut être séparé sans affecter la stabilité de la substance ni modifier sa composition.

-« préparations » : les mélanges ou solutions composées de deux substances ou plus.

2-DETERMINATION DES PROPRIETES DANGEREUSES DES PREPARATIONS :

Selon l'article 3, premier paragraphe de la directive 1999/45/CE du Parlement Européen et du Conseil du 31 Mai 1999, l'évaluation des dangers d'une préparation est fondée sur la détermination :
-des propriétés physico-chimiques
-des propriétés ayant des effets pour la santé
-des propriétés environnementales.

Selon l'article 6 et les annexes II et III de la directive 1999/45/CE, ce sont tous les effets sur la santé de chacune des substances connues qui doivent être évalués.
La toxicité des préparations étant établie par rapport à leurs différents composants, les essais toxicologiques ne sont pas nécessaires pour la classification des préparations.

3-ANNEXES :

-annexe A : directive 67/548/CEE du Conseil du 27 Juin 1967 concernant le rapprochement des dispositions législatives, réglementaires et administratives relatives à la classification, l'emballage et l'étiquetage des substances dangereuses

-annexe B : directive 1999/45/CE du Parlement Européen et du Conseil du 31 Mai 1999 concernant le rapprochement des dispositions législatives, réglementaires et administratives des Etats membres relatives à la classification , l'emballage et l'étiquetage des préparations dangereuses reprise par l'OChim

4-CENTRE ANTI POISON :

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II-ETUDE TOXICOLOGIQUE des principes actifs NORASYSTEM®

Dans le cadre d'une utilisation normale, les différents principes actifs NORASYSTEM® ne présentent aucune toxicité par inhalation, par ingestion et ne provoquent aucune irritation cutanée.

II-1 TOXICITE ORALE

Produits NORASYSTEM®	Dose habituelle d'utilisation	Dose maximale d'utilisation	DL 50	Coefficient de sécurité par rapport à la DL50*	Commentaires
NORASYSTEM® 301	**0.0068%**	**1.19%**	**2000 mg/kg**	**97**	**calcul pour un homme de 70 kg pour une application détergence avec une quantité de 1.44 g de produit dans une dosette de 120 g**
NORASYSTEM® 302	**0.0015%**	**9.6%**	**2000 mg/k**	**292**	**calcul pour un homme de 70 kg pour une application de dépôt de 5 g de produit sur un filtre**
NORASYSTEM® 304	**0.5%**	**0.5%**	**2000 mg/kg**	**28**	**calcul pour un homme de 70 kg pour une application détergence avec une quantité de 5 g de produit dans un litre**
NORASYSTEM® 305	**0.07%**	**1.19%**	**2000 mg/kg**	**12**	**calcul pour un homme de 70 kg pour une application détergence avec une quantité de 11.9 g de produit dans un litre**
NORASYSTEM® 306	**0.1%**	**9.6%**	**1225 mg/kg**	**178**	**calcul pour un homme de 70 kg pour une application de dépôt de 5 g de produit sur un filtre**

*Le coefficient de sécurité est le rapport entre la dose maximale d'exposition en se plaçant dans les conditions extrêmes et la DL50.

II-2 TOXICITE PAR INHALATION

Produits NORASYSTEM®	Dose habituelle d'utilisation	Dose maximale d'utilisation	DL 50	Coefficient de sécurité par rapport à la DL50	Commentaires
NORASYSTEM® 301	0.0068%	1.19%	-		Pas de toxicité
NORASYSTEM® 302	0.0015%	9.6%	-		Pas de toxicité
NORASYSTEM® 304	0.5%	0.5%	-		Pas de toxicité
NORASYSTEM® 305	0.07%	1.19%	-		Pas de toxicité
NORASYSTEM® 306	0.1%	9.6%	3760 mg/kg	548	calcul pour un homme de 70 kg pour une application de dépôt de 5 g de produit sur un filtre

II-3 TOXICITE DERMIQUE

Produits NORASYSTEM®	Dose habituelle d'utilisation	Dose maximale d'utilisation	DL 50	Coefficient de sécurité par rapport à la DL 50	Commentaires
NORASYSTEM® 301	0.0068%	1.19%	2000 mg/kg	97	
NORASYSTEM® 302	0.0015%	9.6%	2000 mg/kg	292	
NORASYSTEM® 304	0.5%	0.5%	-		Pas de toxicité
NORASYSTEM® 305	0.07%	1.19%	-		Pas de toxicité
NORASYSTEM® 306	0.1%	9.6%	2000 mg/kg	292	

II-4 IRRITATION OCCULAIRE

Produits NORASYSTEM®	Dose habituelle d'utilisation	Dose maximale d'utilisation	Résultat
NORASYSTEM® 301	0.0068%	1.19%	Irritation
NORASYSTEM® 302	0.0015%	9.6%	Irritation
NORASYSTEM® 304	0.5%	0.5%	Pas d'irritation
NORASYSTEM® 305	0.07%	1.19%	Pas d'irritation
NORASYSTEM® 306	0.1%	9.6%	Irritation

II-5 ECOTOXICITE

Produits NORASYSTEM®	ECOTOXICITE CE 50 i-24 h
NORASYSTEM® 301	0.85 mg/l
NORASYSTEM® 302	Pas de données
NORASYSTEM® 304	Pas de données
NORASYSTEM® 305	60 mg /l
NORASYSTEM® 306	Pas de données

Les principes actifs dans le cadre d'une utilisation normale ne présentent aucun caractère toxique.

Les études toxicologiques sont jointes en annexe:
-annexe 2A: étude toxicologique du NORASYSTEM® 301
-annexe 2B: étude toxicologique du NORASYSTEM® 302
-annexe 2C: étude toxicologique du NORASYSTEM® 304
-annexe 2D: étude toxicologique du NORASYSTEM® 305
-annexe 2E: étude toxicologique du NORASYSTEM® 306

I-DEFINICION DE LA TOXICIDAD

1-SUSTANCIAS Y PREPARACIONES :

Según el artículo 2, primero parágrafo, alinea a et b de la directiva 1999/45/CE del Parlamento Europeo y del Consejo del 31 de Mayo 1999, las sustancias y preparaciones son definidas de la manera siguiente:

-« sustancias » : los elementes químicos y los suyos compuestos en natural estado o tales cuales obtenidos con todo procedimiento de producción, incluido todo aditivo necesario para preservar la estabilidad del producto y toda impureza derivando del procedimiento, pero a la exclusion de todo solvente quien puede ser separado sin cambiar la estabilidad de la sustancia y sin cambiar su composición.

-« preparaciones » : las mezclas o soluciones compuestas de dos sustancias o mas.

2-DETERMINACION DE LAS PROPIEDADES PELIGROSAS DE LAS PREPARACIONES :

Según el artículo 3, primero parágrafo de la directiva 1999/45/CE del Parlamento Europeo y del Consejo del 31 de Mayo 1999, la evaluación de los peligros de una preparación es fundada en la determinación:
-de las propiedades físico-químicas
-de las propiedades actuando sobre la salud
-de las propiedades medioambientales.

Según el articulo 6 y los anexos II et III de la directiva 1999/45/CE, todos los efectos sobre la salud de cada las sustancia conocidas deben ser evaluados.
La toxicidad de las preparaciones estando establecida en relación con los suyos diferentes componentes, los ensayos toxicológicos no son necesarios para la clasificación de las preparaciones.

3-ANEXOS :

-anexo A : directiva 67/548/CEE del Consejo del 27 de Junio 1967 relativo al acercamiento de las disposiciones legislativas, reglamentarias y administrativas para la clasificación, el embalaje y el etiquetado de las sustancias peligrosas

-anexo B : directiva 1999/45/CE del Parlamento Europeo y del Consejo del 31 de Mayo 1999 relativo al acercamiento de las disposiciones legislativas, reglamentarias y administrativas de los Estados miembros para la clasificación, el embalaje y el etiquetado de las preparaciones peligrosas reemprendida por el OChim

II-ESTUDIO TOXICOLOGICO de los principios activos NORASYSTEM®

En el caso de una normal utilización, los differentes principios activos NORASYSTEM® no presentan ninguna toxicidad por inhalación, por ingestión y no provocan ninguna dérmica irritación.

II-1 ORAL TOXICIDAD

Productos NORASYSTEM®	Dosis habitual de utilización	Dosis maximal de utilización	DL 50	Coeficiente de seguridad con relación a la DL50*	Comentarios
NORASYSTEM® 301	**0.0068%**	**1.19%**	**2000 mg/kg**	**97**	**cálculo por un hombre de 70 kg para una aplicación detergente con una cantidad de 1.44 g de producto en una dosis de 120 g**
NORASYSTEM® 302	**0.0015%**	**9.6%**	**2000 mg/k**	**292**	**cálculo por un hombre de 70 kg para una aplicación de deposito de 5 g de producto sobre un filtro**
NORASYSTEM® 304	**0.5%**	**0.5%**	**2000 mg/kg**	**28**	**cálculo por un hombre de 70 kg para una aplicación détergente con una cantidad de 5 g de producto en un litro**
NORASYSTEM® 305	**0.07%**	**1.19%**	**2000 mg/kg**	**12**	**cálculo por un hombre de 70 kg para une aplicación détergente con una cantidad de 11.9 g de producto en un litro**
NORASYSTEM® 306	**0.1%**	**9.6%**	**1225 mg/kg**	**178**	**cálculo por un hombre de 70 kg para una aplicación de deposito de 5 g de producto sobre un filtro**

*El coeficiente de seguridad es la relación entre la dosis maximal de exposición estando en condiciones extremas y la DL50.

II-2 TOXICIDAD POR INHALACION

Productos NORASYSTEM®	Dosis habitual de utilización	Dosis maximal de utilización	DL 50	Coeficiente de seguridad con relación a la DL50	Comentarios
NORASYSTEM® 301	0.0068%	1.19%	-		No toxicidad
NORASYSTEM® 302	0.0015%	9.6%	-		No toxicidad
NORASYSTEM® 304	0.5%	0.5%	-		No toxicidad
NORASYSTEM® 305	0.07%	1.19%	-		No toxicidad
NORASYSTEM® 306	0.1%	9.6%	3760 mg/kg	548	cálculo por un hombre de 70 kg para una aplicación de deposito de 5 g de producto sobre un filtro

II-3 DERMICA TOXICIDAD

Productos NORASYSTEM®	Dosis habitual de utilización	Dosis maximal de utilización	DL 50	Coeficiente de seguridad con relación a la DL 50	Comentarios
NORASYSTEM® 301	0.0068%	1.19%	2000 mg/kg	97	
NORASYSTEM® 302	0.0015%	9.6%	2000 mg/kg	292	
NORASYSTEM® 304	0.5%	0.5%	-		No toxicidad
NORASYSTEM® 305	0.07%	1.19%	-		No toxicidad
NORASYSTEM® 306	0.1%	9.6%	2000 mg/kg	292	

II-4 IRRITACION DE LOS OJOS

Productos NORASYSTEM®	Dosis habitual de utilización	Dosis maximal de utilización	Resultado
NORASYSTEM® 301	0.0068%	1.19%	Irritación
NORASYSTEM® 302	0.0015%	9.6%	Irritación
NORASYSTEM® 304	0.5%	0.5%	No irritación
NORASYSTEM® 305	0.07%	1.19%	No irritación
NORASYSTEM® 306	0.1%	9.6%	Irritación

II-5 ECOTOXICIDAD

Productos NORASYSTEM®	ECOTOXICIDAD CE 50 i-24 h
NORASYSTEM® 301	0.85 mg/l
NORASYSTEM® 302	No datos
NORASYSTEM® 304	No datos
NORASYSTEM® 305	60 mg /l
NORASYSTEM® 306	No datos

Los principios activos en el caso de una utilización normal no presentan ningún toxico carácter.

Los estudios toxicológicos son añadidas en en anexo:
-anexo 2A: estudio toxicológico de NORASYSTEM® 301
-anexo 2B: estudio toxicológico de NORASYSTEM® 302
-anexo 2C: estudio toxicológico de NORASYSTEM® 304
-anexo 2D: estudio toxicológico de NORASYSTEM® 305
-anexo 2E: estudio toxicológico de NORASYSTEM® 306

I-TOXICITY DEFINITION

1-SUBSTANCES and PREPARATIONS:

In accordance with the article 2, first paragraph, alinea a and b of the European Parliament directive 1999/45/CE and of the 31st of May 1999 Council, the substances and the preparations are notified in the following way:

-« substances » : chemical elements and their compounds in a natural condition or such as, get by any process of production, even every additives necessary to preserve the stability of the product and every impurities coming from the process, but exception of every solvent separable without modifying the stability of the substance and without modifying its composition.

-« preparations »: the mixtures or solutions composed with two substances or more.

2-DETERMINATION OF DANGEROUS PROPERTIES OF THE PREPARATIONS:

In accordance with the article 3, first paragraph of the European Parliament directive 1999/45/CE and of the 31st of May 1999 Council, the evaluation of the dangers of a preparation is based on the determination of:
-Physic-chemical properties
-health reacting effect properties
-environmental properties.

In accordance with the article 6 and the annexes II and III of the directive 1999/45/CE, all the les effects on health of each of the known substances must be evaluated.
The toxicity of the preparations established in accordance with their different components, the toxicological tests are not necessary for the classification of the preparations.

3-ANNEXES :

-annex A: directive 67/548/CEE of the 27th of June 1967 Council relating to the bringing together of legislative, statutory and administrative disposals concerning classification, packaging and labelling of dangerous substances

-annex B : directive 1999/45/CE of the 31st of May 1999 European Parliament and Council concerning the bringing together of legislative, statutory and administrative disposals of the States members for classification , packaging and labelling of dangerous preparations picked up again by OChim

II-TOXICOLOGICAL STUDY of the active principles NORASYSTEM®

In a context of a normal use, the different active principles NORASYSTEM® don't present any toxicity by inhalation, by ingestion and don't provoke any coetaneous irritation.

II-1 ORAL TOXICITY

Products NORASYSTEM®	Normal use dosage	Maximum use dosage	LD 50	Safety coefficient in relation to LD50*	Comments
NORASYSTEM® 301	**0.0068%**	**1.19%**	**2000 mg/kg**	**97**	**calculation for a 70kg man for a detergent application with a quantity of 1.44g of product in a measuring cap of 120g**
NORASYSTEM® 302	**0.0015%**	**9.6%**	**2000 mg/k**	**292**	**calculation for a 70kg man for an application of a deposit of 5 g of product on a filter**
NORASYSTEM® 304	**0.5%**	**0.5%**	**2000 mg/kg**	**28**	**calculation for a 70kg man for a detergent application with a quantity of 5 g of product in a litre**
NORASYSTEM® 305	**0.07%**	**1.19%**	**2000 mg/kg**	**12**	**calculation for a 70kg man for a detergent application with a quantity of 11.9 g of product in a litre**
NORASYSTEM® 306	**0.1%**	**9.6%**	**1225 mg/kg**	**178**	**calculation for a 70kg man for an application of a deposit of 5 g of product on a filter**

*The safety coefficient is the relation between the maximum exposure dosage setting in the most extreme conditions and LD50.

II-2 INHALATION TOXICITY

Products NORASYSTEM®	Normal use dosage	Maximum use dosage	LD 50	Safety coefficient in relation to LD50	Comments
NORASYSTEM® 301	0.0068%	1.19%	-		No toxicity
NORASYSTEM® 302	0.0015%	9.6%	-		No toxicity
NORASYSTEM® 304	0.5%	0.5%	-		No toxicity
NORASYSTEM® 305	0.07%	1.19%	-		No toxicity
NORASYSTEM® 306	0.1%	9.6%	3760 mg/kg	548	calculation for a 70 kg man for an application of a deposit of 5 g of product on a filter

II-3 DERMAL TOXICITY

Products NORASYSTEM®	Normal use dosage	Maximum use dosage	LD 50	Safety coefficient in relation to LD 50	Comments
NORASYSTEM® 301	0.0068%	1.19%	2000 mg/kg	97	
NORASYSTEM® 302	0.0015%	9.6%	2000 mg/kg	292	
NORASYSTEM® 304	0.5%	0.5%	-		No toxicity
NORASYSTEM® 305	0.07%	1.19%	-		No toxicity
NORASYSTEM® 306	0.1%	9.6%	2000 mg/kg	292	

II-4 EYES IRRITATION

Products NORASYSTEM®	Normal use dosage	Maximum use dosage	Result
NORASYSTEM® 301	0.0068%	1.19%	Irritation
NORASYSTEM® 302	0.0015%	9.6%	Irritation
NORASYSTEM® 304	0.5%	0.5%	No irritation
NORASYSTEM® 305	0.07%	1.19%	No irritation
NORASYSTEM® 306	0.1%	9.6%	Irritation

II-5 ECOTOXICITY

Products NORASYSTEM®	ECOTOXICITY CE 50 i-24 h
NORASYSTEM® 301	0.85 mg/l
NORASYSTEM® 302	No data
NORASYSTEM® 304	No data
NORASYSTEM® 305	60 mg /l
NORASYSTEM® 306	No data

The active principles in a context of a normal use don't present any toxic characteristic.

The toxicological studies are put in annex:
-annex 2A: toxicological study of NORASYSTEM® 301
-annex 2B: toxicological study of NORASYSTEM® 302
-annex 2C: toxicological study of NORASYSTEM® 304
-annex 2D: toxicological study of NORASYSTEM® 305
-annex 2E: toxicological study of NORASYSTEM® 306

"The informations given in this document are based on our present knowledge, in the updating date. They are given in a complete faith. The user on its own responsibility must check the conditions and the possibilities of use for this product following the legislative and reglementary disposals in use. Our responsibility cannot be bound in a case of unusual use of the product"

ANNEXE 2A: étude toxicologique de NORASYSTEM® 301

TOXICITY : NORASYSTEM® 301

Name : NORASYSTEM® 301

Producer related part
Company : Phode
Creation date : 09.08.2001

Substance related part
Company : Phode
Creation date : 09.08.2001

Number of pages : 12

1 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

1.1 ACUTE ORAL TOXICITY

Type	:	LD0
Value	:	> 2000 mg/kg bw
Species	:	rat
Strain	:	Sprague-Dawley
Sex	:	male/female
Number of animals	:	10
Vehicle	:	other: none
Doses	:	2000 mg/kg
Method	:	OECD Guide-line 401 "Acute Oral Toxicity"
Year	:	1987
GLP	:	yes
Test substance	:	other TS

Method : The test substance was administered to a group of 10 fasted Sprague-Dawley rats (5 males and 5 females). The administration was performed with the test substance in its original form at a dose level of 2000 mg/kg taking into consideration that the specific gravity (SG) of the test substance was 1.032.
The mortality, general behaviour and bodyweight gain of the animals were observed for a period of 14 days after the single administration of the test substance. A necropsy was performed on each animal sacrificed at the end of the study.

Result : There was no mortality at the dose level of 2000 mg/kg.
The general behaviour of the animals was not influenced by the treatment.
A clear bodyweight loss was observed in one female between D 1 and D 5 without any effect on behaviour and any influence thereafter on the study. The bodyweight gain of the other animals was normal throughout the study.
The macroscopic examination revealed no abnormality in the animals sacrificed at the end of the study.

Conclusion : NORASYSTEM® 301(in a 33.2% aqueous solution) administered by oral route in the Rat was higher than 2000 mg/kg, i.e. higher than 664 mg/kg of pure NORASYSTEM® 301. No signs of toxicity were observed at this dose level.

Reliability : (1) valid without restriction

21.03.2002 (1)

1.2 ACUTE INHALATION TOXICITY

1.3 ACUTE DERMAL TOXICITY

Type	:	LD50
Value	:	> 2000 mg/kg bw
Species	:	rat
Strain	:	Sprague-Dawley
Sex	:	male/female
Number of animals	:	10

Vehicle	:	other: none
Doses	:	2000 mg/kg
Method	:	OECD Guide-line 402 "Acute dermal Toxicity"
Year	:	1987
GLP	:	yes
Test substance	:	other TS
Method	:	The test substance was applied in its original form at a dose level of 2000 mg/kg taking into consideration that the specific gravity (SG) of the test substance was 1.032 and directly to the skin of 10 Sprague-Dawley rats (5 males and 5 females). The test substance was held in contact with the skin by means of a semi-occlusive dressing for 24 hours. The mortality, general behaviour and bodyweight gain of the animals were observed for a period of 14 days after the single application of the test substance. A necropsy was performed on each animal found dead during the study or sacrificed at the end of the study.
Result	:	There was a 20% mortality rate at the dose level of 2000 mg/kg. It appeared on D 2 (2 females). No apparent symptoms were observed prior to death which was possibly to experimental stress caused by the dressing. The general behaviour and bodyweight gain of the animals were not influenced by the treatment. The macroscopic examination revealed no abnormalities in the animals found dead during the study or sacrificed at the end of the study.
Conclusion	:	NORASYSTEM® 301 (in a 33.2% aqueous solution) administered by dermal route in the Rat was higher than 2000 mg/kg, i.e. higher than 664 mg/kg of pure NORASYSTEM® 301. A 20% mortality rate was observed at this dose level.

21.03.2002 (2)

1.4 ACUTE TOXICITY, OTHER ROUTES

2.1 SKIN IRRITATION

Species	:	rabbit
Concentration	:	undiluted
Exposure	:	Semiocclusive
Exposure time	:	4 hour(s)
Number of animals	:	3
Vehicle	:	
PDII	:	
Result	:	irritating
Classification	:	irritating
Method	:	OECD Guide-line 404 "Acute Dermal Irritation/Corrosion"
Year	:	1981
GLP	:	yes
Test substance	:	other TS
Method	:	A single dose of 0.5 ml of the test substance in its original form was prepared on a gauze patch and then appl i ed to a 6 cm2 clipped area of 3 male New Zealand rabbits. First of all, the test was performed using one animal in order to check that the result by cutaneous route was non-existant to moderate. The test was continued using 2

		other animals 72 hours after the cutaneous application in the first animal. The test substance was held in contact with the skin for 4 hours by means of a semi-occlusive dressing. The cutaneous reactions were observed 1 hour, 24, 48 and 72 hours after removal of the dressing and then daily in order to observe their reversibility or irreversibility.
Result	:	One hour then 24, 48 and 72 hours after removal of the dressing, slight to well defined cutaneous reactions (erythema) were observed in all animals. In 2 animals, the erythema remained well defined for 72 hours. No oedema was noted. On the following days, the lesions were reversible and totally di sappeared on D 6 i n one animal and on D 11 i n the two remaining animals. Dryness of the skin was also noted in two animals from D 6 until the end of the study (D 11).
Conclusion	:	NORASYSTEM® 301 (in a 33.2% aqueous solution) was considered as irritant by cutaneous route in the Rabbit.
Reliability	:	(1) valid without restriction

21.03.2002 (3)

2.2 EYE IRRITATION

Species	:	rabbit
Concentration	:	
Dose	:	.1 ml
Exposure time	:	
Comment	:	
Number of animals	:	3
Vehicle	:	
Result	:	irritating
Classification	:	irritating
Method	:	OECD Guide-line 405 "Acute Eye Irritation/Corrosion"
Year	:	1987
GLP	:	yes
Test substance	:	other TS
Method	:	A single dose of 0.1 ml of the test substance was instilled into the conjunctival sac of the left eye of one male New Zealand White rabbit. The ocular reactions were observed 1 hour, 24, 48 and 72 hours after the instillation and then daily in order to observe their reversibility or irreversibility. Due to the ocular reactions recorded in this animal, the study was not undertaken in 2 other animals.
Result	:	One hour after instillation of the test substance, marked conjunctival reactions were observed. After 24 and 48 hours, the conjunctival lesions remained marked. A congestion of the iris and a slight corneal opacity were also noted. After 72 hours, the conjunctival reactions became severe. The iridian and corneal lesions persisted. The ocular reactions regressed clearly after one week (D 8). The reversibility of lesions was confirmed on the following days and no further ocular reactions were noted on D 11.
Conclusion	:	NORASYSTEM® 301 (in a 33.2% aqueous solution) is considered as irritant in the Rabbit. The ocular lesions were more marked after 72 hours and were totally reversible on the eleventh day of observation.
Reliability	:	(1) valid without restriction

21.03.2002 (4)

3 SENSITIZATION

Type	:	Guinea pig maximization test
Species	:	guinea pig
Concentration	:	1st: Induction .1 % intracutaneous 2nd: Induction 50 % occlusive epicutaneous 3rd: Challenge 50 % occlusive epicutaneous
Number of animals	:	30
Vehicle	:	other: 0.9% sodium chloride
Result	:	not sensitizing
Classification	:	not sensitizing
Method	:	OECD Guide-line 406 "Skin Sensitization"
Year	:	1981
GLP	:	yes
Test substance	:	other TS

Method :

Thirty guinea-pigs (15 males and 15 females) were allocated to 2 groups: a control group (5 males and 5 females) and a treated group (10 males and 10 females).
The sensitization potential of the test substance was evaluated after a 10-day induction period, during which the animals were treated with the vehicle (control group) or the test substance (treated group). On D 1, 0.1 ml of test substance was administered by intraderm al route at a concentration of 0.1% in a 0.99 NaCl isotonic solution. On D 9, this was applied by cutaneous route diluted at 50%. After a 15-day rest period, a challenge cutaneous application of 0.5 ml of the vehicle (left flank) and the test substance diluted at 50% (right flank) was administered to all animals. The substances were held in contact with the skin for 24 hours by means of an occlusive dressing. The cutaneous reactions were evaluated at the challenge application site, 24 and 48 hours after removal of the dressing.
After the final scoring, the animals were sacrificed and cutaneous samples were taken from the challenge application sites in all animais. Due to the absence of any "doubtful" macroscopic cutaneous reactions, no histological examination was performed on the cutaneous samples.

Result : No symptoms or mortality were observed throughout the study. Twenty-four and 48 hours after removal of the dressing from the cutaneous challenge application, no reactions were observed.

Conclusion : According to the maximization method of magnusson and kligman, no cutaneous reactions due to any sensitization process of the substance NORASYSTEM® 301 (in a 33.2% aqueous solution) were observed in the guinea-pig.

Reliability : (1) valid without restriction

21.03.2002 (5)

4 REPEATED DOSE TOXICITY

Type	:	
Species	:	rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	gavage

Exposure period	:	14 days
Frequency of treatm.	:	daily
Post exposure period	:	none
Doses	:	50, 250, 1000 mg/kg/d
Control group	:	yes, concurrent vehicle
Method	:	other: range-finding study
Year	:	
GLP	:	yes
Test substance	:	other TS: NORASYSTEM® 301, 33% solution

Method :

The potential toxicity of NORASYSTEM® 301 was evaluated, when administered daily by oral route (gavage) to Sprague-Dawley rats for 2 weeks.

Three groupe of 6 male and 6 female Sprague-Dawley rats received, NORASYSTEM® 301 (33% w/w aqueous solution), daily by gavage at the dose-levers of 50, 250 or 1000 mg/kg/day (expressed in acid) for 2 weeks. The test substance was administered in the vehicle (purified water), as a solution. An additional group of 6 males and 6 females received purified water alone under the same conditions and acted as a control group. The animals were checked daily for clinical signs and mortality. Body weight and food consumption were recorded twice or three times a week. At the end of the treatment period, the animals were killed. Selected organs were weighed. All animals were submitted to a full macroscopic post mortem examination, almost all tissue specimens were preserved and a microscopic examination was carried out on:
. all macroscopic lesions of the first five surviving animals of all groups and of animals killed prematurely or found dead during the study.
. kidneys, liver and stomach with forestomach of the first five surviving animals of the control, intermediate and high dose-level groups and of all an animals killed prematurely or found dead during the study.

Result :

Ptyalism and loud breathing were observed from the beginning of the treatment period, in one male given 250 mg/kg/day and in all animals given 1000 mg/kg/day. Signs of poor clinical conditions were noted at the end of the treatment period in a few animals given 50 or 250 mg/kg/day (on to three per group); they were more marked and noted in almost all the animals given 1000 mg/kg/day. One male was killed prematurely and three females were found dead at 1000 mg/kg/day, from day l0. Slight to markedly lonwer food consumption and body weight gain were noted in males given 250 or 1000 mg/kg/day and in the surviving females given 1000 mg/kg/day.

There were no differences from controls that could be attributed to treatment with the test substance haematological parameters.At the high dose-level of 1000 mg/kg/day, slight to moderately higher urea lever (in both sexes), associated with slightly higher creatinine lever in females, was recorded. In view of the absence of significant renal histopathological changes, the high urea lever might be due to low glomerular filtration rate.

No notable differences from controls were recorded on organ weights. The forestomach was thickened in almost all animals receiving 1000 mg/kg/day. At the high dose-level of 1000 mg/kg/day, epithelial cell hyperplasia and hyperkeratosis together with mucosal and submucosal oedema in the forestomach and oedema in the submucosa of the stomach (in males only) were observed.

Conclusion :

The daily administration of NORASYSTEM® 301, at the dose-levers of 0, 50, 250 or 1000 mg/kg/day, by gavage to rats for a 2-week period caused dose related signs of toxicity from the low dose-level. At 50 mg/kg/day, signs of poor clinical condition were noted in only one male and two females. At 250 and 1000 mg/kg/day, this was associated with ptyalism and loud breathing, lonwer body weight gain and food consumption

(incidence related to the dose-lever). In addition at 1000 mg/kg/day, mortality, higher urea and creatinine levers and signs of stomacal irritation were noted. Consequently, the No Observed Effect Level was not established.

Reliability : (1) valid without restriction
21.03.2002 (6)

Type	:	
Species	:	rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	gavage
Exposure period	:	13 weeks
Frequency of treatm.	:	daily
Post exposure period	:	4 weeks
Doses	:	20, 60, 180/360 mg/kg/d
Control group	:	yes, concurrent vehicle
NOAEL	:	= 60 mg/kg bw
Method	:	OECD Guide-line 408 "Subchronic Oral Toxicity - Rodent: 90-day Study"
Year	:	1981
GLP	:	yes
Test substance	:	other TS: NORASYSTEM® 301, 33% solution

Method : The potential toxicity of NORASYSTEM® 301 was evaluated, following daily oral administration (gavage) to rats for 13 weeks, followed by a four-week treatment-free period for the control and high-dose group.

A total of 120 Sprague-Dawley rats (60 males and 60 females) were randomly allocated to four groups (three treated and one control group) of ten males and ten females Bach, with the exception of the control and high-dose groups (20 males and 20 females).
The test substance in aqueous solution was administered daily by gavage at the dose-levers of 20, 60 or 180/360 mg/kg/day, for 13 weeks (180 mg/kg/day until day 50 and 360 mg/kg/day thereafter); the dosing was split in two administrations with a 3 to 4 hours interval. The control animals were given the vehicle (purified water) under the same experimental conditions.
The first nine surviving males and ten surviving females of the control group, and the first nine surviving males and eight surviving females of the high dose group, were kept for a 4-week treatment-free period.
The animals were checked daily for mortality, morbidity and clinical signs. Body weight was recorded before allocation of the animals to the group, on the first day of treatment, and then once a week until the end of the study. Food and water consumption was recorded over a seven-day period, once a week until the end of the study.
Ophthalmological examinations were performed on all animals of the control and high-dose groups, once before the beginning and at the end of the treatment period.
Hematological, blood biochemical and urinary investigations were performed on the first ten surviving animals of each sex and group, at the end of the treatment period and for some blood biochemical parameters at the end of the treatment-free period. On completion of the treatment and treatment-free periods, all animals were submitted to a complete macroscopic post-mortem examination and selected organs were weighed. Macroscopic lesions and specified tissues were preserved. Microscopic examination was performed for all animals on specified tissues and macroscopic lesions.

Result : There were no mortality attributed to a toxic effect of the test substance. Ptyalism was noted with dose-relationship in animals given 60 and 180/360 mg/kg/day. Loud breathing was noted in some females given 60 mg/kg/day and almost all animals given 180/360 mg/kg/day; at 180/360 mg/kg/day, this often correlated with signs of poor clinical condition and signs of

respiratory difficulties.

A lower body weight gain correlating with a longer food consumption was noted in males given 180/360 mg/kg/day, following the change of dose-lever in week 8. There were no noteworthy differences on efficiency of food consumption in any group. There were no noteworthy differences in water consumption in any group.

There were no noteworthy ophthalmological findings in any group. No relevant differences between treated and control animals were observed on haematological parameters. Lower glucose and triglyceride plasma levels were noted in all treated females. Partial (triglyceride) or total (glucose) reversibility was observed at the end of the treatment-free period. There were no noteworthy differences from controls in any treated group on urinalysis.

There were no noteworthy differences between treated and control animals on organ weights. No treatment-related macroscopic findings were noted in treated animals. Minimal to moderate degenerative cardiomyopathy was noted in some animals given 180/360 mg/kg/day, but with a longer incidence and severity at the end of the treatment-free period than at the end of the treatment period. Thus indicating partial reversibility.

Conclusion : When administered daily by gavage (in two administrations) in rats at the dose-levers of 20, 60 or 180/360 mg/kg/day, for 13 weeks, NORASYSTEM® 301, was well tolerated at 20 mg/kg/day. At 60 mg/kg/day, ptyalism noted in almost all the animals was not considered an adverse effect. At 180/360 mg/kg/day, ptyalism sometimes associated with respiratory difficulties and signs of poor clinical condition, lower body weight gain and food consumption in males following the change of dose leler and some minor changes in glucose and triglyceride plasma levels in females were noted. The target organ was the heart in which a degenerative cardiomyopathy was seen in the high-dose group. Reversibility was recorded for all affected parameters or organs. Consequently under the laboratory conditions, the NOAEL was 60 mg/kg/day.

Reliability : (1) valid without restriction
21.03.2002 (7)

5 GENETIC TOXICITY 'IN VITRO'

Type : Salmonella typhimurium reverse mutation assay
System of testing : TA98, TA100, TA1535, TA1537, TA1538
Test concentration : 10, 50, 100, 500 and 1000 µg/plate
Cycotoxic concentr. : >= 2500 µg/plate
Metabolic activation : with and without
Result : negative
Method : OECD Guide-line 471
Year :
GLP : yes

Reliability : (1) valid without restriction
21.03.2002 (8)

Type : Mammalian cell gene mutation assay
System of testing : V79 Chinese hamster cells
Test concentration : 0.10, 0.25, 0.50, 0.75 and 1.00 mg/ml without S9 mix and of 0.05, 0.10, 0.25, 0.50, 0.75 and 1.00 mg/ml with S9 mix
Cycotoxic concentr. : >1 mg/ml
Metabolic activation : with and without
Result : negative

Method	:	OECD Guide-line 476
Year	:	1984
GLP	:	yes
Test substance	:	other TS
Method	:	The in vitro mutagenic activity of the test substance NORASYSTEM® 301 was investigated in the V79 Chinese hamster cells. The test system V79/HPRT allows to detect at the HPRT locus (hypoxanthine-phosphoribosyl-transferase) base-pair mutations, frameshift mutations and small deletions. After a preliminary cytotoxicity assay, performed to define the range dose levels to be used for the mutagenicity test, the test substance was tested in the absence and in the presence of a metabolic activation system, the S9 mix, in 2 separate assays. The concentrations were of 0.10, 0.25, 0.50, 0.75 and 1.00 mg/ml without S9 mix and of 0.05, 0.10, 0.25, 0.50, 0.75 and 1.00 mg/ml with S9 mix.
Result	:	No mutagenic effect was observed in this test system V79/HPRT either without or with the S9 mix system at the concentrations used. The mutation frequency of cells treated with the positive reference compounds: N-methyl-N-nitro-N-nitrosoguanidine without S9 mix or dimethylnitrosamine with S9 mix was higher than the mutation frequency of untreated cells, indicating the sensitivity of the test system as well as the efficacy of the metabolic activation system.
Conclusion	:	NORASYSTEM® 301 is not mutagenic in the Chinese hamster V79/HPRT gene mutation assay.
Reliability	:	(1) valid without restriction
21.03.2002		(9)

Type	:	Cytogenetic assay
System of testing	:	human lymphocytes
Test concentration	:	400, 600 and 800 µg/ml
Cycotoxic concentr.	:	>= 800 µg/ml
Metabolic activation	:	with and without
Result	:	ambiguous
Method	:	OECD Guide-line 473
Year	:	
GLP	:	yes
Reliability	:	(1) valid without restriction
21.03.2002		(10)

Type	:	Unscheduled DNA synthesis
System of testing	:	rat hepatocytes in vitro
Test concentration	:	5, 10, 25, 50, 100 and 250 µg/ml
Cycotoxic concentr.	:	>= 500 µg/ml
Metabolic activation	:	without
Result	:	negative
Method	:	OECD Guide-line 482
Year	:	
GLP	:	yes
Reliability	:	(1) valid without restriction
21.03.2002		(11)

6 GENETIC TOXICITY 'IN VIVO'

Type	:	Micronucleus assay
Species	:	mouse
Sex	:	male/female
Strain	:	CD-1
Route of admin.	:	gavage
Exposure period	:	Sacrifice at 24, 48 and 72 hours after the single administration or at 24 and 48 hours after the 2nd of the double administration
Doses	:	Single administration: 700, 1400, 2800, 4500 mg/kg Double administration: 1700 mg/kg
Result	:	negative
Method	:	OECD Guide-line 474 "Genetic Toxicology: Micronucleus Test"
Year	:	
GLP	:	yes
Reliability	:	(1) valid without restriction

21.03.2002 (12)

Type	:	other: Cytogenetic assay in bone marrow
Species	:	hamster
Sex	:	male/female
Strain	:	
Route of admin.	:	i.p.
Exposure period	:	single administration
Doses	:	37.5, 75 and 150 mg/kg
Result	:	negative
Method	:	OECD Guide-line 475 "Genetic Toxicology: In vivo Mammalian Bone Marrow Cytogenetic Test - Chromosomal Analysis"
Year	:	1984
GLP	:	yes
Test substance	:	other TS
Method	:	The clastogenic activity of NORASYSTEM® 301 was investigated in bone marrow cells of Chinese hamsters after a single intraperitoneal injection. Numerical and structural chromosomal aberrations were scored in the cells at the metaphase stage. The test substance NORASYSTEM® 301 was administered at the three dose levels of 37.5, 75 and 150 mg/kg bodyweight, the high dose level being the maximum tolerated dose in this species. Animal treated with the vehicle (sterile saline physiological solution) acted as negative controls. The bone marrow was sampled 6, 24 and 48 hours after administration. Animals treated with cyclophosphamide by intraperitoneal route at the dose level of 80 mg/kg bodyweight acted as positive controls, the bone marrow was sampled 24 hours after administration.
Result	:	Cyclophosphamide induced a highly significant increase in the number of aberrant cells and chromosomal aberrations indicating the sensitivity of the test system. The rate of aberrations observed with NORASYSTEM® 301 was similar to that observed in the negative controls at each sacrifice period.
Conclusion	:	NORASYSTEM® 301 is not clastogenic in the bone marrow of the Chinese hamster in vivo.
Reliability	:	(1) valid without restriction

21.03.2002 (13)

7 CARCINOGENICITY

8.1 TOXICITY TO FERTILITY

8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

9 SPECIFIC INVESTIGATIONS

10 EXPOSURE EXPERIENCE

11 ADDITIONAL REMARKS

(1) NORASYSTEM® 301. ACUTE ORAL TOXICITY STUDY IN THE RAT. CIT Evreux.

(2) NORASYSTEM® 301. ACUTE DERMAL TOXICITY STUDY IN THE RAT. CIT Evreux.

(3) NORASYSTEM® 301. DERMAL IRRITATION STUDY IN THE RABBIT. CIT Evreux.

(4) NORASYSTEM® 301. EYE IRRITATION STUDY IN THE RABBIT. CIT Evreux.

(5) NORASYSTEM® 301. SENSITIZATION TEST IN THE GUINEA-PIG. CIT Evreux.

(6) NORASYSTEM® 301. Preliminary 2-week toxicity study by oral administration (gavage) in rats. CIT .

(7) NORASYSTEM® 301. 13-week toxicity study by oral administration (gavage) in rats followed by a 4-week treatment-free period. CIT.

(8) NORASYSTEM® 301, SANOFI.

(9) NORASYSTEM® 301. HPRT GENE MUTATION ASSAY IN V79 CHINESE HAMSTER CELLS. CIT Evreux.

(10) NORASYSTEM® 301, Microtest.

(11) NORASYSTEM® 301, SANOFI,

(12) NORASYSTEM® 301, SANOFI,

(13) NORASYSTEM® 301. CHROMOSOMAL ANALYSIS OF CHINESE HAMSTER BONE MARROW CELLS. CIT Evreux.

ANNEXE 2B: étude toxicologique de NORASYSTEM® 302

TOXICITY :
NORASYSTEM® 302

Name	:	NORASYSTEM® 302
Producer related part		
Company	:	Phode
Creation date	:	08.08.2001
Substance related part		
Company	:	Phode
Creation date	:	08.08.2001
Number of pages	:	8

1 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

1.1 ACUTE ORAL TOXICITY

Type	:	LD0
Value	:	>= 2000 mg/kg bw
Species	:	rat
Strain	:	Sprague-Dawley
Sex	:	male/female
Number of animals	:	10
Vehicle	:	other: corn oil
Doses	:	
Method	:	OECD Guide-line 401 "Acute Oral Toxicity"
Year	:	1987
GLP	:	yes
Test substance	:	other TS

Method : The test substance was administered by oral route (gavage) to one group of ten fasted Sprague-Dawley rats (five males and five females).
The test substance was prepared in corn oil and administered to the animals at the dose of 2000 mg/kg, under a volume of 10 ml/kg.
Clinical signs, mortality and body weight gain were checked for a period of up to 14 days following the single administration of the test substance.
All animals were subjected to necropsy.

Result : No deaths occurred at 2000 mg/kg.
Hypoactivity and piloerection were recorded in one male and one female on day 1 only. The general behaviour of the other animals was not affected by treatment with the test substance.
A slight body weight loss was noted in one female between days 8 and 15. The body weight gain of the other animals were not affected by treatment with the test substance.
No apparent abnormalities were observed at necropsy in all animals.

Conclusion : Under our experimental conditions, the oral LDO of the test substance NORASYSTEM® 302 is equal to or higher than 2000 mg/kg in rats.

09.08.2001 (1)

1.2 ACUTE INHALATION TOXICITY

1.3 ACUTE DERMAL TOXICITY

Type	:	LD0
Value	:	>= 2000 mg/kg bw
Species	:	rat
Strain	:	Sprague-Dawley
Sex	:	male/female
Number of animals	:	10
Vehicle	:	
Doses	:	

Method	:	OECD Guide-line 402 "Acute dermal Toxicity"
Year	:	1987
GLP	:	yes
Test substance	:	other TS
Method	:	The test substance was applied in its original form at the dose of 2000 mg/kg to the skin of one group of ten Sprague-Dawley rats (five males and five females). The test site was then covered by a semi-occlusive dressing for 24 hours. Clinical signs, mortality and body weight gain were checked for a period of 14 days following the single application of the test substance. All animals were subjected to necropsy.
Result	:	No death occurred at 2000 mg/kg. The general behaviour and body weight gain of the animals were not affected by treatment with the test substance. No cutaneous reactions were observed. No apparent abnormalities were observed at necropsy in all animals.
Conclusion	:	Under our experimental conditions, the dermal LDo of the test substance NORASYSTEM® 302 is equal to or higher than 2000 mg/kg in rats. No signs of toxicity were observed at this dose.

09.08.2001 (2)

1.4 ACUTE TOXICITY, OTHER ROUTES

2.1 SKIN IRRITATION

08.08.2001

2.2 EYE IRRITATION

Species	:	rabbit
Concentration	:	
Dose	:	100 other: mg
Exposure time	:	
Comment	:	not rinsed
Number of animals	:	3
Vehicle	:	
Result	:	slightly irritating
Classification	:	irritating
Method	:	OECD Guide-line 405 "Acute Eye Irritation/Corrosion"
Year	:	1987
GLP	:	yes
Test substance	:	other TS
Method	:	The study design was established according to available information on the test substance and the above guidelines. As possible irritant effects were anticipated, the test substance was administered to a single male New Zealand White rabbit in the first instance. Since the test substance was not severely irritant in this first animal, it was administered to two other animals.

		A single dose of 100 mg of the test substance in its original form was introduced into the left conjunctival sac. The right eye was not treated and served as control. The eyes were not rinsed after administration of the test substance. Ocular reactions were observed approximately 1 hour, 24, 48 and 72 hours after the administration and then daily until reversibility of the ocular reactions. The mean values of the scores for chemosis, redness of the conjunctiva, iris lesions and corneal opacity were calculated for each animal.
Result	:	Very slight to moderate conjunctival reactions (very slight to moderate chemosis, very slight or slight redness of the conjunctiva and clear to whitish purulent discharge) were observed in all animals from day 1; these reactions persisted up to day 14 at the latest. A slight iritis was noted in two animals on day 2; it persisted up to day 4 or 10. A very slight or slight corneal opacity was recorded in all animals on day 2; it persisted up to day 4 (two animals) or 12 (one animal). Mean scores calculated for each animal over 24, 48 and 72 hours were 3.0, 2.0 and 2.7 for chemosis, 2.0, 1.7 and 2.0 for redness of the conjunctiva, 1.0, 0.0 and 1.0 for iris lesions and 1.7, 1.0 and 1.0 for corneal opacity.
Conclusion	:	Under our experimental conditions, the test substance NORASYSTEM® 302 is irritant when administered by ocular route to rabbits.

09.08.2001 (3)

3 SENSITIZATION

4 REPEATED DOSE TOXICITY

5 GENETIC TOXICITY 'IN VITRO'

Type	:	DNA damage and repair assay
System of testing	:	Hépatocytes de rat (Fischer)
Test concentration	:	
Cycotoxic concentr.	:	
Metabolic activation	:	
Result	:	negative
Method	:	OECD Guide-line 482
Year	:	
GLP	:	yes
Test substance	:	other TS
Method	:	Produit: NORASYSTEM® 302 Système cellulaire: Hépatocytes de rat (Fischer) en culture primaire Concentrations(µg/ml): . Etude cytoxicité: 1-10-50-100-500 et 1000 µg/ml . Etudes de génotoxicité: - 1ère étude: 1-5-10-25-50 et 100 µg/ml - 2ème étude: 10-25-50 et 100 µg/ml

Solvant: Diméthylsulfoxyde

Nombre d'études: 2: CEL330 et CEL330B

Témoin positif: 2-aminofluorène (0.1 et 0.5 µM)

Result : Cytoxique à 500 et 1000 µg/ml.
Non génotoxique aux doses de 25,50 et 100 µg/ml.

Conclusion : Non génotoxique in vitro dans le test de réparation de l'ADN.

09.08.2001 (4)

Type : Salmonella typhimurium reverse mutation assay
System of testing : Salmonella typhimurium: TA 98, TA 100, TA 1535, TA 1537, TA 1538
Test concentration :
Cycotoxic concentr. :
Metabolic activation : with and without
Result : negative
Method : OECD Guide-line 471
Year :
GLP : yes
Test substance : other TS

Method : Compound: NORASYSTEM® 302

Tester strains: Salmonella typhimurium: TA98, TA100, TA1535, TA1537, TA 1538

Concentrations (µg/plate):
. Bacterial toxieity study: 100, 250, 500, 750, 1000, 2500 and 5000
. Genotoxicity study: 10, 50, 100, 250, 500 and 750

Solvent: DMSO (Dimethylsulfoxide)

No. plates/concentration/Study: 3

No. of studies: 2: CEL273A and CEL273B

Metabolic activation: S-9 from Aroclor 1254-induced rat liver (10%)

Positive controls:
. Without metabolic activation:
- Na azide: 5 µg/plate (TA100, TA1535)
- 2-nitrofluorene: 5 µg/plate (TA98, TA 1538)
- 9-aminoacndine: 20 µg:'plate (TA1537)
. With metabolic activation:
- 2-ammoanthracene: 5 µg/plate

Result : Toxic: 1000, 2500 and 5000 µ/plate
Non mutagenic: 10, 50, 100, 250, 500 and 750 µg/plate, with and without metabolic activation on the 5 tester strains

Conclusion : No genotoxic activity on Salmonella typhimurium

09.08.2001 (5)

Type : Mammalian cell gene mutation assay
System of testing : V79 Chinese hamster cells
Test concentration :
Cycotoxic concentr. :
Metabolic activation : with and without
Result : negative
Method : OECD Guide-line 476

Year	:	1984
GLP	:	yes
Test substance	:	other TS
Method	:	The in vitro mutagenic activity of the test substance NORASYSTEM® 302 was investigated in the V79 Chinese hamster cells. The test system V79/HPRT allows to detect at the HPRT locus (hypoxanthine-phosphoribosyl-transferase) base-pair muta-tions, frameshift mutations and small deletions. After a preliminary cytotoxicity assay, performed to define the range dose levels to be used for the mutagenicity test, the test substance was assayed in the absence and in the presence of a metabolic activation system, the S9 mix, in 2 separate assays. The concentrations were of: 10, 30, 100, 300 and 500 µg/ml for the Ist assay without S9 mix and for both tests with S9 mix and of 30, 100, 300, 400, 500 and 600 µg/ml for the tnd assay without S9 mix.
Result	:	No mutagenic effect was observed in this test system V79/HPRT either without or with the S9 mix system at the concentrations used. The mutation frequency of cells treated with the positive reference compounds: N-methyl-N-nitro-N-nitrosoguanidine without S9 mix or dimethylnitrosamine with S9 mix was higher than the mutation frequency of untreated cells, indicating the sensitivity of the test system as well as the efficacy of the metabolic activation system.
Conclusion	:	Under the described experimental conditions, the test substance NORASYSTEM® 302 is not mutagenic in the Chinese hamster V79/HPRT gene mutation assay.

09.08.2001 (6)

Type	:	Chromosomal aberration test
System of testing	:	Human lymphocyte
Test concentration	:	
Cycotoxic concentr.	:	
Metabolic activation	:	with and without
Result	:	negative
Method	:	OECD Guide-line 473
Year	:	
GLP	:	yes
Test substance	:	other TS
Result	:	Treatment of cells with NORASYSTEM® 302 in both the absence and presence of S-9 resulted in numbers of aberrations which were similar to those observed in concurrent negative controls. A small but statistically significant increase in structural and numerical aberrations at 500 µg/ml in the absence of S-9 was seen but was not considered to be biologically significant because historical solvent control ranges were not exceeded at this treatment level nor under any other treatment conditions.
Conclusion	:	It is concluded that NORASYSTEM® 302 was unable to induce chromosome aberrations in human lymphocytes when tested to its limit of solubility in either the absence or presence of S-9.

09.08.2001 (7)

6 GENETIC TOXICITY 'IN VIVO'

Type	:	Micronucleus assay

Species	:	mouse
Sex	:	male/female
Strain	:	ICR
Route of admin.	:	oral unspecified
Exposure period	:	
Doses	:	
Result	:	negative
Method	:	OECD Guide-line 474 "Genetic Toxicology: Micronucleus Test"
Year	:	
GLP	:	yes
Test substance	:	other TS

Method : Compound: NORASYSTEM® 302

Species/strain: CD1 (ICR) BR mouse

Route of administration: Oral

solvent: 10% gum arabic solution

Dosage (g/kg): 1,2 and 4

Positive control: Cyclophosphamide (60 mg/kg by the intraperitoneal route in physiological saline)

Number of animals/group: 15 M, 15F

Number of administrations: 1

Sacrifice epochs: 24,48 and 72 hours following treatment

Slides examined: Those obtained after 24 and 48 hours.

Result : No medullary cytotoxicity.
No increase of polychromatic micronucleated erythrocytes at the 3 dose levels studied.

Conclusion : No genotoxic activity in vivo.

09.08.2001 (8)

7 CARCINOGENICITY

8.1 TOXICITY TO FERTILITY

8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

9 SPECIFIC INVESTIGATIONS

10 EXPOSURE EXPERIENCE

11 ADDITIONAL REMARKS

(1) NORASYSTEM® 302 ACUTE ORAL TOXICITY IN RATS. CIT Evreux.

(2) NORASYSTEM® 302. ACUTE DERMAL TOXICITY IN RATS. CIT Evreux.

(3) NORASYSTEM® 302. ACUTE EYE IRRITATION IN RABBITS. CIT Evreux.

(4) NORASYSTEM® 302. Test de réparation de l'ADN in vitro sur des cultures primaires d'hépatocytes de rat. SANOFI RECHERCHE, Montpellier.

(5) NORASYSTEM® 302. REVERSE MUTATION ASSAY ON SALMONELLA TYPHIMURIUM. SANOFI RECHERCHE, Montpellier.

(6) NORASYSTEM® 302. HPRT GENE MUTATION ASSAY IN V79 CHINESE HAMSTER CELLS. CIT Evreux.

(7) NORASYSTEM® 302. Study to evaluate the potential of NORASYSTEM® 302 by its effects on cultured human lymphocytes using an in vitro cytogenics assay. Microtest Research Limited, United Kingdom.

(8) NORASYSTEM® 302. IN VIVO GENOTOXICITY STUDY OF UNDECYLENIC ACID BY THE ORAL ROUTE IN THE MOUSE. SANOFI RECHERCHE, Montpellier.

ANNEXE 2C: étude toxicologique de NORASYSTEM® 304

TOXICITY :
NORASYSTEM® 304

FICHE DE DONNEES DE SECURITE
Selon la directive 2001/58/CEE

NORASYSTEM® 304

1. IDENTIFICATION DE LA SUBSTANCE/PREPARATION ET DE LA SOCIETE/ENTREPRISE

Identité chimique Acide gras

Fournisseur **PHODE**
ZAC Albipôle
81150 ALBI TERSSAC
France
Tel.: 05 63 77 80 60

N° Tél. d'urgence ORFILA: 01 45 42 59 59
(INTOXICATIONS)

Emploi prévu Intermédiaire chimique

2. COMPOSITION/INFORMATION SUR LES COMPOSANTS

Ce produit doit être considéré comme une substance selon les directives CE.
Informations sur les composants dangereux

Description chimique Acide gras

Composition / Renseignements sur les ingrédients

Numéro	% en poids	N° CAS	Nom chimique
1	env. 100		NORASYSTEM® 304

3. IDENTIFICATION DES DANGERS

Non classé comme dangereux. Se conformer à la directive CEE sur les substances dangereuses et la directive sur les préparations dangereuses.

4. PREMIERS SECOURS

Symptômes et effets Aucun symptôme typique ni effet connu.

Premiers secours

Généralités En cas de doutes, ou si les symptômes persistent, consulter un médecin.

Inhalation Ceci n'est possible qu'en cas d'exposition au produit CHAUD. Déplacer à l'air frais, mettre au repos, position latérale de sécurité, desserrer les vêtements. Consulter un médecin.

Peau Retirer les vêtements souillés. Consulter un médecin si une irritation apparaît.

Yeux Rincer complètement avec beaucoup d'eau. Les paupières doivent être écartées du globe oculaire pour assurer un rinçage complet. Consulter un médecin si une irritation apparaît.

Ingestion Rincer la bouche à l'eau. Dans les cas graves, appeler le service médical.

Avis aux médecins Ce produit est considéré comme sans peu dangereux pour l'homme.

5. MESURES DE LUTTE CONTRE L'INCENDIE

Moyens d'extinction brouillard d'eau, Mousse, poudre sèche, Dioxyde de carbone.

Produit d'extinction inapproprié Ne jamais utiliser un jet d'eau

Dangers spéciaux d'exposition Pas de recommandations précises.

Produits de décomposition/ combustion dangereux En cas de décomposition thermique, risque de formation de fumées acres.

Equipement de protection Pas de recommandations précises.

6. MESURES A PRENDRE EN CAS DE DISPERSION ACCIDENTELLE

Précautions individuelles	Les précautions usuelles de manipulation des produits chimiques doivent être appliquées.
Précautions pour l'environnement	Pas de recommandations précises.
Méthodes de nettoyage	Recueillir le maximum dans un récipient propre pour réutiliser (de préférence) ou éliminer. Couvrir le reste avec de l'absorbant inerte (de la vermiculite par exemple) pour éliminer ultérieurement.
Autres informations	Pour la protection du personnel, voir la rubrique 8.

7. MANIPULATION ET STOCKAGE

Manipulation	Les précautions usuelles de manipulation des produits chimiques doivent être appliquées.
Prévention des incendies et explosions	Une inflammation spontanée peut se produire en cas de particules fines et chaudes.
Conditions de stockage	Pas de recommandations précises.
Autres informations	normalement stable.

8. CONTROLE DE L'EXPOSITION/PROTECTION INDIVIDUELLE

Contrôles techniques	Les mesures de précautions usuelles de manipulation des produits chimiques doivent être observées.
Limites d'exposition	Une limite d'exposition n'a pas été établie.
Protection personnelle	
Respiratoire	Pas de recommandations précises.
Main	Pas de recommandations précises.
Yeux	Eviter le contact avec les yeux.
Peau et corps	Pas de recommandations précises.
Autres informations	Les précautions usuelles de manipulation des produits chimiques doivent être appliquées.

9. PROPRIETES PHYSIQUES ET CHIMIQUES

Aspect	liquide (20 °C)
Couleur	jaunâtre
Odeur	caractéristique
Point/intervalle d'ébullition	**> 200 °C (100** kPa**)**
Point/intervalle de fusion	env. **0 °C**
Point d'éclair	> 100 °C, Pensky-Martens coupe fermée
Inflammabilité	non concerné
Température d'inflammation spontanée	**> 250 °C**
Propriétés d'explosivité	non déterminé
Limites d'explosivité	non déterminé
Propriétés d'oxydation	non déterminé
Pression de vapeurs	**< 10** Pa **(20 °C)**
Densité	env. **900 kg/m^3 (20 °C)**
Densité en vrac	non concerné
Solubilité dans l'eau	Pratiquement insoluble
Solubilité dans d'autres solvants	Ethanol, hydrocarbures
pH	non concerné
Coefficient de partage n-octanol/eau	non déterminé
Densité relative de la vapeur (air=1)	**10-15** (>250 **°C, 0.05** kPa **)**
Viscosité	env. 500 mPa.s (20 °C)

10. STABILITE ET REACTIVITE

Stabilité normalement stable
Conditions à éviter une inflammation spontanée peut se produire en cas de particules fines et chaudes
Matériaux à éviter

11. INFORMATIONS TOXICOLOGIQUES

Aucune donnée toxicologique sur les produits disponibles pour l'instant. A partir de produits de structure apparentée, on peut s'attendre à:

Nom	**NORASYSTEM® 304**
Toxicité aiguë	
Oral DL50	> 2000 mg/kg (rat)
Irritation	
Peau	non irritant
Yeux	non irritant

12. INFORMATIONS ECOLOGIQUES

Nom Acide gras
Devenir dans l'environnement
Dégradation biotique biodégradable.

13. CONSIDERATIONS RELATIVES A L'ELIMINATION

Produit Selon la réglementation locale (très probablement incinération contrôlée).
Emballage contamin Selon la réglementation locale.

14. INFORMATIONS RELATIVES AU TRANSPORT

Transport terrestre (ADR/RID)

Classement ADR	non restreint	Code de classification ADR	non pertinent pertinent
Classement RID	non restreint	Groupe de conditionnement ADR/RID	
N° d'identification de danger	non pertinent	**N° d'identification de substance**	non pertinent
Carte TREM	non pertinent	**N°UN**	aucun(e)
Dénomination technique	non pertinent		

Transport maritime (IMO/Code IMDG)

IMO/Code IMDG	non restreint	**Classe**	non restreint
Groupe d'emballage	non pertinent	**N°UN**	aucun(e)
EMS	non pertinent	Risques secondaires	non pertinent
Polluant marin	non		
Dénomination technique	non pertinent		

Transport aérien (ICAO-TI/IATA-DGR)

ICAO-TI/IATA-DGR		**N°UN**	aucun(e)
Classe	non restreint	**Groupe d'emballage**	non pertinent
Dénomination technique	non pertinent		

15. INFORMATIONS REGLEMENTAIRES

Description chimique Acide gras

Etiquetage selon directives CEE **N°CE** 2002/06/18 code produit NORASYSTEM®304, date de dernière modification : 2002/06/18

Symbole(s) aucun(e)
Phrases R(isque) aucun(e).
Phrases S(écurité) aucun(e).
Wassergefährdungsklasse (WGK) 1 (VwVwS Anhang 2 No. 659)

16. AUTRES INFORMATIONS

Ces informations ne concernent que le produit susmentionné et ne sont pas nécessairement valables en cas d'utilisation avec d'autre(s) produit(s) ou dans tout procédé. En l'état actuel de nos connaissances, ces informations sont correctes, complètes et données de bonne foi mais sans garantie. La responsabilité de vérifier que les informations sont adéquates et complètes pour son application particulière revient à l'utilisateur lui-même

Information sur les phrases de risque « R »

Nom chimique	Phrases de risques	
NoraSystem®304	aucun(e)	aucun(e)

Historique

Date d'impression	2005/05/23	
Révision	**1.02**	
Composé par	Dr. P. Thomas	S. Kleine
Des modifications ont été faites dans le chapitre	**1**	

ANNEXE 2D: étude toxicologique de NORASYSTEM® 305

TOXICITY :
NORASYSTEM® 305

FICHE DE DONNEES DE SECURITE

(conformément à la directive CEE/93/112)

Version: 1.1

Mise à jour 15.08.2003
Date d'impr. 01.06.2005

NORASYSTEM® 305

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1. IDENTIFICATION DE LA SUBSTANCE/PREPARATION ETDE LA SOCIETE/ENTREPRISE

Marque NORASYSTEM® 305

Fabricant / Fournisseur PHODE France ZAC
Albipôle 81150 ALBI TERSSAC.
Téléphone: 0563778060 Téléfax: 563778061

Division des renseignements

N° téléphonique d'urgence

2 COMPOSITION/INFORMATION SUR LES COMPOSANTS

Caractérisation chimique : NORASYSTEM® 305

3. IDENTIFICATION DES DANGERS

Indications de risque pour l'homme et l'environnement

Pas de dangers particuliers connus.

4. PREMIERS SECOURS

Conseils généraux : Oter les vêtements souillés.

Après inhalation : En cas d'inhalation, faire respirer de l'air frais et demander l'avis d'un médecin.

Après contact cutané : En cas de contact avec la peau, laver immédiatement à l'eau et au savon. En cas d'irritation persistante de la peau, consulter un médecin.

Après contact oculaire : En cas de contact avec les yeux, laver immédiatement et abondamment avec de l'eau et consulter un spécialiste.

Après ingestion : En cas de douleurs, demander un avis médical.

FICHE DE DONNEES DE SECURITE

(conformément à la directive CEE/93/112)

Version: 1.1

Mise à jour 15.08.2003
Date d'impr. 01.06.2005

NORASYSTEM® 305

5. MESURES DE LUTTE CONTRE L'INCENDIE

Moyen d'extinction approprié	mousse, dioxyde de carbone, poudre extinctive, pulvérisation d'eau
Moyen d'extinction à ne pas utiliser pour des raisons de sécurité	non applicable
Risques particuliers dûs au produit, à ses résidus de combustion ou aux gaz produits	En cas d'incendie, il peut y avoir dégagement de: - dioxyde et monoxyde de carbone - Oxyde de zinc Dans certains cas d'incendie, la présence de traces d'autres substances toxiques n'est pas exclue.
Equipements spéciaux pour la protection des intervenants	Ne pas respirer les gaz de combustion en cas d'explosion et d'incendie.

6. MESURES A PRENDRE EN CAS DE DISPERSION ACCIDENTELLE

Précautions individuelles	Utiliser les équipements de protection individuels.
Précautions pour la protection de l'environnement	Ne pas rejeter dans les canalisations d'égout ni dans les eaux d'écoulement. Ne pas rejeter dans la terre/le sous-sol.
Méthodes de nettoyage/récupération	Ramasser avec un produit liant (par ex. sable, Kieselguhr, liant universel). Le produit récupéré doit être éliminé selon la réglementation en vigueur.

7. MANIPULATION ET STOCKAGE

Manipulation

Précautions lors de la manipulation	:	Veiller à la bonne aération des locaux,
Indications pour la protection contre l'incendie et l'explosion	:	Aucune mesure spéciale n'est nécessaire,

Stockage

Information supplémentaire	:	Maintenir les récipients hermétiquement fermés.
Cl.de stockage(RFA)		10

FICHE DE DONNEES DE SECURITE

(conformément à la directive CEE/93/112)

Version:		Mise à jour	15.08.2003
	1.1	Date d'impr.	01.06.2005

NORASYSTEM®305

8. CONTROLE DE L'EXPOSITION/PROTECTION INDIVIDUELLE

Protection individuelle

Mesures d'hygiène	Ne pas manger, boire, fumer, priser sur le lieu de travail. Se laver les mains avant les pauses et au moment de quitter le travail. Enlever immédiatement tout vêtement souillé ou éclaboussé.
Protection respiratoire	S'il y a dégagement de vapeurs/aérosols : en cas de brève exposition, utiliser un masque avec filtre, filtre A/P2
Protection des mains	- gants en PVC
Protection des yeux	lunettes avec protection latérale
Protection de la peau et du corps	- vêtement de protection léger

9. PROPRIETES PHYSIQUES ET CHIMIQUES

Forme	liquide jaune
Couleur	clair
Odeur	caractéristique
température de fusion	non déterminé
température d'ébullition	non déterminé
Point d'éclair	> 100 °C Méthode: DIN 51758
Température d'inflammation	non déterminé
Limite d'explosivité, inférieure	non déterminé
Limite d'explosivité, supérieure	non déterminé
Pression de vapeur	non déterminé env.
Densité	1,1 g/cm3
solubilité dans l'eau	à 20 °C miscible
pH	env. 10 à 20 °C

Viscosité, dynamique	300 mPa.s à 23 °C Méthode: DIN/ISO 6388

10.STABILITE ET REACTIVITE

Décomposition thermique	non déterminé
Réactions dangereuses	Pas de réactions dangereuses si les prescriptions de stockage et de manipulation sont respectées.
Produits de décomposition dangereux	Aucun si les préscriptions de stockage et de manipulation sont respectées.

11.INFORMATIONS TOXICOLOGIQUES

Note : on n'a signalé aucun effet nocif pour la santé du produit manipulé correctement

12.INFORMATIONS ECOLOGIQUES

Autres données écologiques

Note	Le produit est répertorié comme légèrement polluant pour l'eau (loi allemande). Empêcher toute infiltration du produit dans le sol et l'écoulement dans les eaux et les égouts.

13.CONSIDERATIONS RELATIVES A L'ELIMINATION

Produit	compte tenu de la réglementation locale en vigueur, le produit doit être transporté dans une installation d'incinération agréée
Emballages contaminés	Pour le reconditionnement ou l'élimination des emballages vides et contaminés, les preneurs doivent être informés des risques possibles.

14.INFORMATIONS RELATIVES AU TRANSPORT

Transport par route ADR:

Not regulated

RID:

Not regulated

Transport par canaux et rivières

ADNR:

Not regulated

Transport maritime

IMDG:Not regulated

Transport aerien

ICAO/IATA: Not

regulated

15. INFORMATIONS REGLEMENTAIRES

Etiquetage selon la directive CE	Le produit n'est pas soumis à étiquetage selon les Directives communautaires et le GefStoffV (RFA).

Règlements national

VbF (RFA)	Ne relève pas de l'ordonnance sur les liquides combustibles (VbF/RFA).
TA Luft (RFA)	Classe: Paragraphe 5.2.5 (aucune classe)
Classe de danger pour les eaux (WGK;RFA)	1 (Classement selon VwVwS (RFA))
Règlementations particulières	aucun

16. AUTRES INFORMATIONS

aucun

Cette fiche complète la notice technique d'utilisation mais ne la remplace pas. Les renseignements qu'elle contient sont basés sur l'état de nos connaissances et les principaux textes législatifs et réglementaires relatifs au produit et promulgués à la date de conception du document. Les modifications sont marquées devant le chapitre!

ANNEXE 2E: étude toxicologique de NORASYSTEM® 306

TOXICITY :
NORASYSTEM® 306

Name NORASYSTEM® 306

Producer related part
Creation date : 07.08.2001
Phode

Substance related part
Company : Phode
Creation date : 07.08.2001

Number of pages : 65

1 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

1.1 ACUTE ORAL TOXICITY

Type	:	LD50
Value	:	1225 - 1875 mg/kg bw
Species	:	rat
Strain	:	Sprague-Dawley
Sex	:	male/female
Number of animals	:	10
Vehicle	:	other: none
Doses	:	620, 1240, 1860, 2570 mg/kg
Method	:	OECD Guide-line 401 "Acute Oral Toxicity"
Year	:	1981
GLP	:	yes
Test substance	:	other TS

Method :

1. Mode d'administration:
Un premier essai a été effectué avec 5,7 ml/kg, ce qui correspond à la dose maximum administrable de 5000 mg/kg. Une mortalité étant apparue chez les animaux traités, l'essai s'est poursuivi pour la détermination de la DL 50 à des doses inférieures.
Le produit est administré tel quel aux animaux, par voie orale, sous des volumes de 2,9 - 2,1 - 1,4 et 0,7 ml/kg pour chacune des doses, à l'aide d'une sonde oesophagienne.
Les animaux du groupe témoin reçoivent un volume de 5,7 ml/kg du véhicule correspondant au volume maximum administré, aux animaux traités.

2. Posologie et groupes expérimentaux:
Avant de procéder à la détermination de la toxicité aiguë, une étude préliminaire est effectuée sur un nombre réduit d'animaux, afin de rechercher approximativement l'échelle des doses à administrer. Cet essai préalable (dont les résultats ne sont pas mentionnés dans ce rapport) a permis de constituer 4 groupes d'animaux comprenant chacun 5 mâles et 5 femelles traités aux doses suivantes:
2570 - 1860 - 1240 et 620 mg/kg.

3. Modalités du traitement:
La veille du traitement, les animaux sont mis à jeun avant l'administration de celui-ci. Ils sont réalimentés dans les 3 - 4 heures après le traitement.

Result : A la dose de 620 mg/kg, aucune symptomatologie n'est observée. Aux doses supérieures, la symptomatologie apparaît 10 - 15 mn après le traitement : hypocinésie, sédation et coma sont les symptômes dominants.
A la dose de 1240 mg/kg, les animaux sont en hypocinésie.
A la dose de 1860 mg/kg, les animaux sont d'abord en hypocinésie puis en état de sédation.
A la dose de 2570 mg/kg, ils sont en état de sédation puis de coma.
La mortalité survient environ 3 heures après le traitement.
Au Jour 1, la symptomatologie a disparu chez les survivants.
A la dose de 5000 mg/kg, les animaux sont en état de sédation 10 mn après le traitement et de coma 1 heure après

le traitement.
Le détail de la symptomatologie n'est pas reporté dans ce rapport car les résultats obtenus avec cette dose ne sont pas pris en compte dans le calcul de la DL 50.

L'évolution pondérale des animaux survivants n'est pas influencée par le traitement.
L'autopsie des animaux morts en cours d'étude ou euthanasiés en fin d'étude n'a mis en évidence aucune anomalie.

La DL50 est évaluée à 1563 (1225-1875, p=0.05) mg/kg.

Source : Phode, Albi, France.
Reliability : (1) valid without restriction
Flag : Directive 67/548/EEC
16.11.2001 (1)

1.2 ACUTE INHALATION TOXICITY

Type : LC50
Value : 3.25 - 4.1 mg/l
Species : rat
Strain : Wistar
Sex : male/female
Number of animals : 10
Vehicle :
Doses : 2.67, 3.72, 4.54 or 5.48 mg/l
Exposure time : 4 hour(s)
Method : OECD Guide-line 403 "Acute Inhalation Toxicity"
Year : 1993
GLP : yes
Test substance : other TS

Method : The acute (4-hour) inhalation toxicity of NORASYSTEM® 306 was studied by nose-only exposure of four groups of five male and five female rats each to test atmospheres containing 2.67, 3.72, 4.54, or 5.48 g NORASYSTEM® 306 per m3. Nominal concentrations were 2.6, 3.7, 4.5 and 5.9 g/m3, respectively. Particle size measurements showed that at least 95% of the particles was between 1 and including 4.2 µm. After exposure, rats were kept for a 14-day observation period.

Result : Irregular and/or shallow breathing were observed in almost all rats starting from the second hour of exposure. All rats exposed to 5.48 g/m3, 5/5 males and 4/5 females exposed to 4.54 g/m3, and 3/5 males and 2/5 females exposed to 3.72 g/m3 were found dead during the last hour of exposure or shortly thereafter. Clinical signs in survivors shortly after exposure consisted of wet fur in the head- and thorax region; no abnormalities were seen during the 14-day observation period.
No abnormalities in body weight gain were observed in surviving rats, except for marginal body weight gain in most female rats exposed to 2.67 g/m3.
Stiffly closed eyes, white substance in one or two eye chambers, dark and swollen livers and dark discoloured, occasionally blood-containing, lungs were observed in rats that died during or shortly after exposure. Occasional findings consisted of swollen blood vessels in various organs such as stomach, caecum, intestines, testes and/or seminal vesicles. No abnormalities were observed at terminal

sacrifice of the surviving rats 14 days after exposure.

Source	:	Phode, Albi, France.
Conclusion	:	The 4-hour LC50 value of NORASYSTEM® 306 was 3.76 g/m3 with 95%-confidence limits of 3.25 and 4.10 g/m3.
Reliability	:	(1) valid without restriction
Flag	:	Directive 67/548/EEC

16.11.2001 (2)

1.3 ACUTE DERMAL TOXICITY

Type	:	LD0
Value	:	>= 2000 mg/kg bw
Species	:	rat
Strain	:	Sprague-Dawley
Sex	:	male/female
Number of animals	:	10
Vehicle	:	other: none
Doses	:	2000 mg/kg
Method	:	OECD Guide-line 402 "Acute dermal Toxicity"
Year	:	1987
GLP	:	yes
Test substance	:	other TS
Method	:	The test substance was applied to the skin of one group of ten Sprague-Dawley rats (five males and five females). The application was performed with the undiluted test substance at the dose of 2000 mg/kg, taking into consideration that its specific gravity was 0.886 g/ml. The test site was then covered by a semi-occlusive dressing for 24 hours. Clinical signs, mortality and body weight gain were checked for a period of 14 days following the single application of the test substance. All animals were subjected to necropsy.
Result	:	No deaths occurred at 2000 mg/kg. The general behaviour and overall body weight gain of the animals were not affected by treatment with the test substance. No cutaneous reactions were observed. No apparent abnormalities were observed at necropsy in all animals.
Source	:	Phode, Albi, France.
Conclusion	:	The dermal LD0 of NORASYSTEM® 306 is equal to or higher than 2000 mg/kg in rats.
Reliability	:	(1) valid without restriction
Flag	:	Directive 67/548/EEC

16.11.2001 (3)

1.4 ACUTE TOXICITY, OTHER ROUTES

2.1 SKIN IRRITATION

Species	:	rabbit
Concentration	:	undiluted
Exposure	:	Semiocclusive
Exposure time	:	4 hour(s)
Number of animals	:	6

Vehicle	:	
PDII	:	
Result	:	not irritating
Classification	:	not irritating
Method	:	OECD Guide-line 404 "Acute Dermal Irritation/Corrosion"
Year	:	1981
GLP	:	yes
Test substance	:	other TS
Method	:	1. Préparation des animaux: La veille du traitement, les flancs de chaque animal sont tondus sur une surface de peau suffisante avec une tondeuse électrique (Oster, peigne 40 - Laboratoire Méré, 45000 Orléans, France). Seuls sont retenus pour l'étude les animaux présentant une peau parfaitement exempte de toute trace macroscopique d'irritation au moment de l'application, et parfaitement glabre afin que le produit soit toujours en contact avec la peau. 2. Modalités de traitement: 0,5 ml de produit est appliqué sur une surface de 6 cm2 du flanc droit de chaque animal à l'aide d'une seringue en matière plastique de 1 ml graduée en 0,01 ml (Térumo, Polylabo, 67023 Strasbourg, France) et ensuite recouvert d'un carré de gaze hydrophile Codex afin d'éviter toute perte de substance. Le produit et le carré de gaze sont maintenus en contact avec la peau au moyen d'un pansement semi-occlusif : ruban adhésif (laboratoire de Pansements et d'hygiène, 21300 Chenove, France). Le flanc gauche sert de témoin. Le produit est laissé en contact avec la peau pendant 4 heures, les animaux étant placés pendant ce temps dans des boîtes à contention en matière plastique (Iffa-Crédo, 69000 Lyon, France). Ensuite les pansements sont enlevés. Les animaux sont ensuite replacés dans leur cage indi-viduelle.
Result	:	Aucune lésion érythémateuse ou oedémateuse n'est observée pendant la période d'expérimentation.
Source	:	Phode, Albi, France.
Conclusion	:	L'irritation primaire cutanée induite par le produit NORASYSTEM® 306 a été déterminée après application topique sur la peau du lapin Néo-Zélandais. Aucune réaction érythémateuse ou oedémateuse n'est observée. Dans nos conditions expérimentales, le produit est considéré comme non irritant.
Reliability	:	(1) valid without restriction
Flag	:	Directive 67/548/EEC

16.11.2001 (4)

2.2 EYE IRRITATION

Species	:	rabbit
Concentration	:	undiluted
Dose	:	.1 ml
Exposure time	:	
Comment	:	not rinsed
Number of animals	:	6
Vehicle	:	
Result	:	slightly irritating
Classification	:	not irritating

Method	:	OECD Guide-line 405 "Acute Eye Irritation/Corrosion"
Year	:	1981
GLP	:	yes
Test substance	:	other TS
Method	:	1. Préparation des animaux: La veille du traitement, les animaux sont observés de manière à ne garder que ceux exempts de toute atteinte oculaire. 2. Modalités de traitement: 0,1 ml de produit est instillé dans le cul de sac conjonctival inférieur de l'oeil gauche de chaque lapin à l'aide d'une seringue en plastique de 1 ml, graduée en 0,01 ml (Térumo, Polylabo, 67023 Strasbourg, France). Les paupières inférieure et supérieure sont maintenues en contact quelques secondes afin d'éviter toute perte de substance. L'oeil droit ne reçoit aucun produit et sert de témoin. Pour le traitement et pendant les 4 heures suivantes, les animaux sont placés en boîte à contention en matière plastique (Iffa-Credo, 69210 Saint Germain sur l'Arbresle, France).
Result	:	Au niveau conjonctival, un énanthème important apparaît 1 heure après l'instillation chez tous les animaux. Il régresse à partir de J 1 et disparaît à J 2. Au niveau cornéen, à J 1, on note la présence d'une zone d'opacification d'aspect diffus, sur, au plus, un quart de la surface de la cornée, chez quatre animaux (O1, 02, 04 et 06). Aucune réaction iridienne n'est observée. A J 2, ces réactions ont disparu.
Source	:	Phode, Albi, France.
Conclusion	:	l'irritation oculaire induite par le produit NORASYSTEM® 306 a été déterminée après instillation dans le cul de sac conjectival du lapin Néo-Zélandais. Au niveau conjectival, on observe un énanthème important chez tous les animaux, 1 heure après l'instillation. Au niveau cornéen au jour 1, on note une zone d'opacification cornéenne diffuse représentant, au plus, un quart de la surface de la cornée chez quatre animaux. Au jour 2, ces réactions ont disparu. Aucune réaction irridienne n'est relevée. Dans nos conditions expérimentales, le produit est considéré comme légèrement irritant.
Reliability	:	(1) valid without restriction
Flag	:	Directive 67/548/EEC

16.11.2001 (5)

3 SENSITIZATION

Type	:	Guinea pig maximization test
Species	:	guinea pig
Concentration	:	1st: Induction 75 % intracutaneous 2nd: Induction undiluted occlusive epicutaneous 3rd: Challenge undiluted occlusive epicutaneous
Number of animals	:	30
Vehicle	:	other: paraffin oil
Result	:	not sensitizing
Classification	:	not sensitizing

Method	:	OECD Guide-line 406 "Skin Sensitization"
Year	:	1992
GLP	:	yes
Test substance	:	other TS
Method	:	Thirty guinea-pigs were allocated to two groups: a control group 1 (five males and fixe females) and a treated group 2 (ten males and ten females). On day 1, intradermal injections of Freund's complete adjuvant mixed with the test substance (treated group) or the vehicle (control group) were performed in the dorsal region between the shoulders. On day 7, the same region received a topical application of sodium lauryl sulfate in vaseline (10% w/w) in order to induce local irritation. On day 8, this same test site was treated by topical application of the test substance (treated group) or the vehicle (control group) and was covered by an occlusive dressing for 48 hours. On day 22, after a rest period of 12 days, all animals of the treated and control groups were challenged by a topical application of the test substance to the right flank. The left flank served as control and received the vehicle only. Test substance and vehicle were maintained under an occlusive dressing for 24 hours. Skin reactions were evaluated approximately 24 and 48 hours later. Test substance concentrations were as follows: Induction (treated croup) . intradermal injections: NORASYSTEM® 306 at 75% (w/w) in paraffin oil, . topical application: NORASYSTEM® 306 undiluted. Challenge (all groups) . topical application: NORASYSTEM® 306 undiluted. At the end of the study, animals were killed without examination of internal organs. No skin samples were taken from the challenge application sites. The sensitivity of the guinea-pigs was checked with a positive sensitizer: 2,4-DINITRO CHLOROBENZENE (DNCB). During the induction period, the test substance was applied at 0.1% (w/w) (day 1) and 1% (w/w) (day 8). For the challenge application, the DNCB was applied to the right flank at a concentration of 0.5% (w/w).
Result	:	Five females of the treated group were found dead on day 2, following intradermal injections. Hypoactivity and piloerection were noted between day 5 and day 21 in another animal. These mortalities and clinical signs were attributed to the test substance. No clinical signs and no deaths were noted in the remaining animals. No cutaneous reactions were observed after the challenge application. The sensitivity of the guinea-pigs was satisfactory since 50% of the animals showed a positive reaction with DNCB.
Source	:	Phode, Albi, France.
Conclusion	:	According to the maximization method of Magnusson and Kligman, no cutaneous reactions attributable to the sensitization potential of the test substance NORASYSTEM® 306 were observed in guinea-pigs.
Reliability	:	(1) valid without restriction
Flag	:	Directive 67/548/EEC

16.11.2001 (6)

4 REPEATED DOSE TOXICITY

5 GENETIC TOXICITY 'IN VITRO'

Type	:	Salmonella typhimurium reverse mutation assay
System of testing	:	Strains: TA 1535, TA 1537, TA 102, TA 100, TA 98
Test concentration	:	see freetext
Cycotoxic concentr.	:	see freetext
Metabolic activation	:	with and without
Result	:	negative
Method	:	OECD Guide-line 471
Year	:	1983
GLP	:	yes
Test substance	:	other TS

Method :

A preliminary toxicity test was performed to define the doses to be used for the mutagenicity study. The test substance was then tested in two independent tests, with or without a metabolic activation system, the S9 mix, prepared from a liver microsomal fraction (S9) of rats induced with Aroclor 1254.
The tests were performed according to the direct plate incorporation method except the second test with S9 mix, according to the preincubation method (1 hour, 37°C).
Five strains of bacteria Salmonella typhimurium: TA 1535, TA 1537, TA 98, TA 100 and TA 102 were used. Each strain was exposed to 5 doses of the test substance (3 plates/dose).
After 48 to 72 hours of incubation at 37°C, the revertant colonies were scored.
The test substance NORASYSTEM® 306 was dissolved in dimethylsulfoxide (DMSO) or in ethanol.
The doses of the NORASYSTEM® 306 were:
. first test without S9 mix:
- 125, 250, 500, 1000 or 2000 µg/plate. Moderate to marked toxicity was observed at all the doses tested in the TA 1535, TA 1537 and TA 100 strains. A complementary test was performed on these 3 strains at 1, 3, 10, 30 or 100 µg/ml. Under these conditions, no tox-icity was observed.
. Therefore, a second test was performed using the following doses:
- 12.5, 25, 50, 100 or 200 µg/plate.
Moderate to marked toxicity was observed between 25 and 200 pg/plate in the TA 1535, TA 1537 and TA 98 strains. In the TA 100 or TA 102 strains, slight to moderate toxicity was noted between 50 and 200 µg/plate.
Due to the difference in toxicity, DMSO was used instead of ethanol in a third test. The following doses were used:
. TA 1535 and TA 100 strains: 15, 50, 150, 500 or 1500 µg/plate,
. TA 1537, TA 98 or TA 102 strains: 50, 150, 500, 1500 or 5000 µg/plate.
Except in TA 100 strain, moderate to marked toxicity was recorded between 50 and 5000 µg/plate. A complementary test was performed using lower doses:
. TA 1535 and TA 102 strains: 3, 10, 30, 100 and 300 µg/plate,

. TA 1537 strain: 1.5, 5, 15, 50 and 150 µg/plate,
. TA 98 strain: 5, 15, 50, 150 and 500 µg/plate.
Marked toxicity was still noted at doses higher than 10 µg/plate in the TA 102 strain, than 30 µg/plate in the TA 1535 strain and at 150 pg/plate in the TA 1537 strain. In the TA 98 strain, only slight toxicity was noted at 50, 150 or 500 µg/plate.

With S9 mix, the doses were as follows:
. 125, 250, 500, 1000 or 2000 µg/plate in the first test: moderate toxicity was noted at 2000 µg/plate (decrease in the number of revertants),
. 12.5, 25, 50, 100 or 200 µg/plate in the second test: marked toxicity was noted at 100 or 200 µg/plate.

Using DMSO as vehicle, the doses were as follows:
. 15, 50, 150, 500 or 1500 pg/plate (except for the TA 102 strain: 50, 150, 500, 1500 or 5000 µg/plate).
Moderate toxicity was noted at the top dose used, i.e. 150 or 5000 µg/plate.
Each top dose was the dose which showed moderate toxicity.
The doses of the positive controls were as follows:
without S9 mix:
. 1 µg/plate of sodium azide (NaN3): TA 1535 and TA 100 strains,
. 50 µg/plate of 9-Aminoacridine (9AA): TA 1537 strain,
. 0.5 µg/plate of 2-Nitrofluorene (2NF): TA 98 strain,
. 0.5 µg/plate of Mitomycin C (MMC): TA 102 strain.
with S9 mix:
. 2 µg/plate of 2-Anthramine (2AM): TA 1535, TA 1537, TA 98 and TA 100 strains,
. 30 µg/plate of Danthron (DTH): TA 102 strain.

Result : The control results were equivalent to those usually obtained in our Laboratory. The number of revenants induced by the positive controls was higher than the controls, indicating the sensitivity of the test system.
The test substance NORASYSTEM® 306 did not induce any significant increase in the number of revertants, with or without S9 mix, in any of the 5 strains.

Source : Phode, Albi, France.

Conclusion : NORASYSTEM® 306 did not show mutagenic activity in the reverse mutation assay on Salmonella typhimurium. However, variable results of toxicity were obtained.

Reliability : (1) valid without restriction

16.11.2001 (7)

Type : Chromosomal aberration test
System of testing : lymphocyte
Test concentration : see freetext
Cycotoxic concentr. : see freetext
Metabolic activation : with and without
Result : negative
Method : OECD Guide-line 473
Year : 1997
GLP : yes
Test substance : other TS

Method : The test substance was tested in two independent experiments, both with and without a metabolic activation system, the S9 mix, prepared from a liver microsomal fraction (S9 fraction) of rats induced with Aroclor 1254.

No preliminary cytotoxicity test was performed. Dose-levels were selected on the basis of pH, osmolality and solubility.
A wide-range of treatment-levels was used for the first experiment and dose-levels for scoring of chromosomal aberrations were selected on the basis of cytotoxicity indicated by reduction of mitotic index (MI).
For each culture, heparinised whole blood was added to culture medium containing a mitogen (phytohaemagglutinin) and incubated at 37°C in a humidified atmosphere of 5% CO2 / 95% air, for 48 hours.

First experiment
Lymphocyte cultures were exposed to the test or control substances, with or without S9 mix, for three hours then rinsed. Cells were harvested 20 hours after the beginning of treatment, corresponding to approximately 1.5 normal cell cycles. One and a half hours before harvest, each culture was treated with a colcemid solution (10 µg/ml) to block cells at the metaphase-stage of mitosis.
As this first experiment was negative, the study was continued with a second experiment.

Second experiment
. without S9 mix, cells were exposed continuously to the test or control substances.
. with S9 mix, cells were exposed to the test or control substances for three hours and then rinsed.
Cells were harvested 20 hours and 44 hours after the beginning of treatment, corresponding to approximately 1.5 normal cell cycles and 24 hours later, respectively. One and a half hours before harvest, each culture was treated with a colcemid solution (10 µg/ml) to block cells at the metaphase-stage of mitosis.

For both experiments, after hypotonic treatment (KCl 0.075 M), the cells were fixed in a methanollacetic acid mixture (3/1; v/v), spread on glass slides and stained with Giemsa.
All the slides were coded for scoring.
The test substance was dissolved in ethanol.
The dose-levels of the positive controls were as follows:
. without S9 mix, mitomycin C: 3 µg/ml (3 hours of treatment) or 0.2 µg/ml (continuous treatment),
. with S9 mix, cyclophosphamide: 50 µg/ml.

Result **:** In the culture medium, at the end of treatment, the dose-level of 10 mM (corresponding to 1982.7 µg/ml) showed a slight to moderate emulsion. At this dose-level, the pH and the osmolality were equivalent to those of the vehicle control.

Experiments without S9 mix:
With a treatment volume of 15 µl/5.5 ml culture medium, the treatment-levels were as follows:
. 0.078, 0.156, 0.3125, 0.625, 1.25, 2.5, 5 and 10 mM, for the first experiment,
. 0.625, 1.25, 2.5, 5, 7.5 and 10 mM, for the second experiment in both harvest times.

Cytotoxicity:
No toxicity or a slight to strong toxicity were noted, depending on the duration of the exposure to the test substance.
Chromosomal aberration analysis: The analysis of metaphases

was performed at the following dose-levels:
10, 5 and 2.5 mM, in the first experiment (3 hours of treatment),
5, 2.5 and 1.25 mM, in the second experiment at the 20-hour harvest time,
7.5 mM, in the second experiment at the 44-hour harvest time.
The highest dose4evel being either the highest readable dose used for treatment and/or a dose-level inducing more than 50% decrease in the mitotic index, as recommended by the international guidelines.
The test substance did not induce any significant increase in the frequency of cells with chromosome aberrations in both experiments and at both harvest times.

Experiments with S9 mix:
With a treatment volume of 15 µl/5.5 ml culture medium, the treatment-levels were as follows:
0.078, 0.156, 0.3125, 0.625, 1.25, 2.5, 5 and 10 mM, for the first experiment,
0.3125, 0.625, 1.25, 2.5, 5 and 7.5 mM, for the second experiment in both harvest times.

Cytotoxicity:
A slight to strong decrease in the mitotic index was noted generally at dose-levels >= 1.25 mM, depending on the harvest times.
Chromosomal aberration analysis: The analysis of metaphases was performed at the following dose-levels:
10, 5 and 2.5 mM, in the first experiment,
5, 2.5 and 1.25 mM, in the second experiment at the 20-hour harvest time,
1.25 mM, in the second experiment at the 44-hour harvest time.
The highest dose-level being either the highest readable dose and/or a dose-level inducing more than 50% decrease in the mitotic index, as recommended by the international guidelines.
At the 20-hour harvest time, a slight but a significant increase in the frequency of aberrant cells (3%, $p < 0.05$) was noted in the second experiment at 5 mM. This slight increase was however not considered as biologically relevant since it was not noted in the first experiment neither at the same dose-level nor at the higher dose of 10 mM.
At the 44-hour harvest time, the test substance did not induce any significant increase in the frequency of cells with chromosome aberrations.
The frequencies of cells with structural chromosome aberrations of the vehicle and positive controls were as specified in acceptance criteria. The study was therefore considered valid.

Source : Phode, Albi, France.

Conclusion : NORASYSTEM® 306 does not induce chromosome aberrations in cultured human lymphocytes.

Reliability : (1) valid without restriction

16.11.2001 (8)

6 GENETIC TOXICITY 'IN VIVO'

7 CARCINOGENICITY

8.1 TOXICITY TO FERTILITY

8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

9 SPECIFIC INVESTIGATIONS

10 EXPOSURE EXPERIENCE

11 ADDITIONAL REMARKS

(1) NORASYSTEM® 306 ACUTE ORAL TOXICITY IN RAT. CIT Evreux.

(2) NORASYSTEM® 306. ACUTE INHALATION TOXICITY IN RATS. TNO Nutrition and Food Research. TNO report

(3) NORASYSTEM® 306. ACUTE DERMAL TOXICITY IN RATS. CIT Evreux.

(4) NORASYSTEM® 306. ACUTE DERMAL IRRITATION/CORROSION IN RABBIT. CIT Evreux.

(5) NORASYSTEM® 306. ACUTE EYE IRRITATION/CORROSION IN RABBIT. CIT Evreux.

(6) NORASYSTEM® 306. SKIN SENSITIZATION TEST IN GUINEA-PIGS. CIT Evreux.

(7) NORASYSTEM® 306. REVERSE MUTATION ASSAY ON BACTERIA SALMONELLA TYPHIMURIUM. CIT EVREUX.

(8) NORASYSTEM® 306. IN VITRO MAMMALIAN CHROMOSOME ABERRATION TEST IN CULTURED HUMAN LYMPHOCYTES. CIT Evreux.