3.5.2 Gross and histopathology

[redacted]

3.5.3 Other examinations

[redacted]

3.5.4 Statistics

[redacted]

3.6 Further remarks

4 RESULTS AND DISCUSSION

4.1 Observations

4.1.1 Clinical signs

[redacted]

4.1.2 Mortality

[redacted]

4.2 Body weight gain

[redacted]

4.3 Food consumption and compound intake

[redacted]

4.4 Ophtalmoscopic examination

[redacted]

4.5 Blood analysis

4.5.1 Haematology

[redacted]

4.5.2 Clinical chemistry

[redacted]

4.5.3 Urinalysis

[redacted]

4.6 Sacrifice and pathology

4.6.1 Organ weights

[redacted]

4.6.2 Gross and histopathology

[redacted]

[redacted]

4.7 Other

[redacted]

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

[redacted]

5.2 Results and discussion

No particular differences on general condition and behaviour of animals were observed, except of three animals with otitis media (two in the 0.5 mg/kg dose-group and one in the control group) and some animals with dyspnoic symptoms in different groups. No significant difference persisted in body weights. Feed consumption of the females in the 1 mg/kg group was higher compared to the control group.

38 animals died, with an increased number in the group with the highest dosage.
Haemoglobin, haematocrit and erythrocyte counts were decreased in the higher-dosage groups, which seemed to be substance related effects in contrast to the changes in the white blood cells.
Changes in urea nitrogen, alkaline phosphatase and leucine amino peptidase were not dose-related and seemed therefore not to be caused by the treatment with the test material.
Treatment-related decrease of the cholinesterase activity, which would indicate a reduction of the liver function, was not detected
After 5 weeks an increase of the cholesterol content was detected and the content of gamma-globuline decreased in the last part of the investigation period. Both effects seem to be treatment-related.
In every dosage-group the lung weights of the males were increased, the lung weights of the females were increased in the 0.5 mg/kg dosage group. The reason for this effect can be an adaptive reaction.
Histopathological examinations revealed no changes in treated animals.

In one animal of the 1mg/kg dosage-group, which died during the examination period a liver dystrophy, was detected. This could be treatment-related, but to prove this fact only one incident is not sufficient.

5.3 Conclusion

5.3.1 LO(A)EL [redacted]

5.3.2 NO(A)EL [redacted]

5.3.3 Other

5.3.4 Reliability [redacted]

5.3.5 Deficiencies [redacted]

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	[redacted]
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	NOAEL = 1 mg aluminium phosphide/kg bw/d based on increased mortality at the LOAEL of 2 mg/kg bw/d.
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]
	COMMENTS FROM ... *(specify)*

Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

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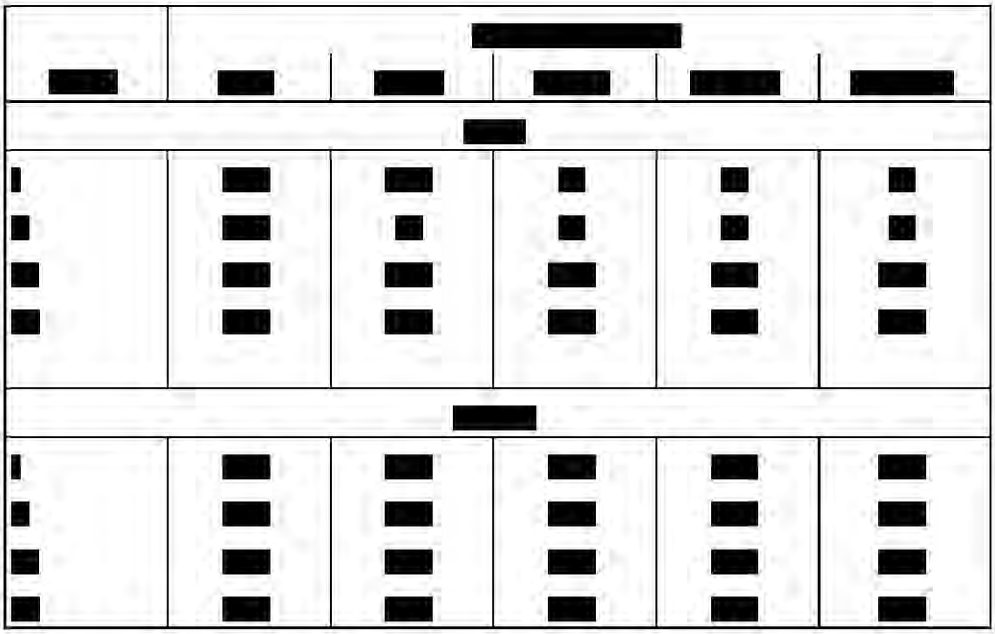

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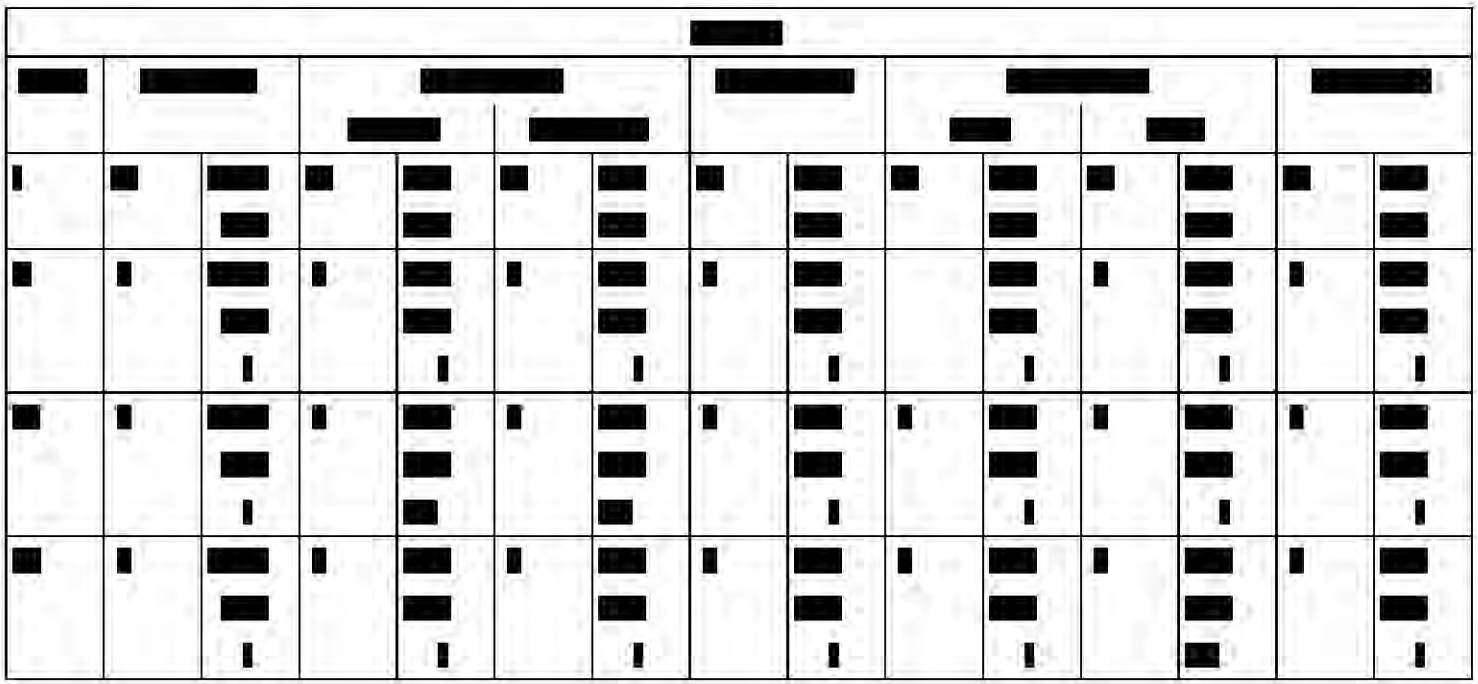

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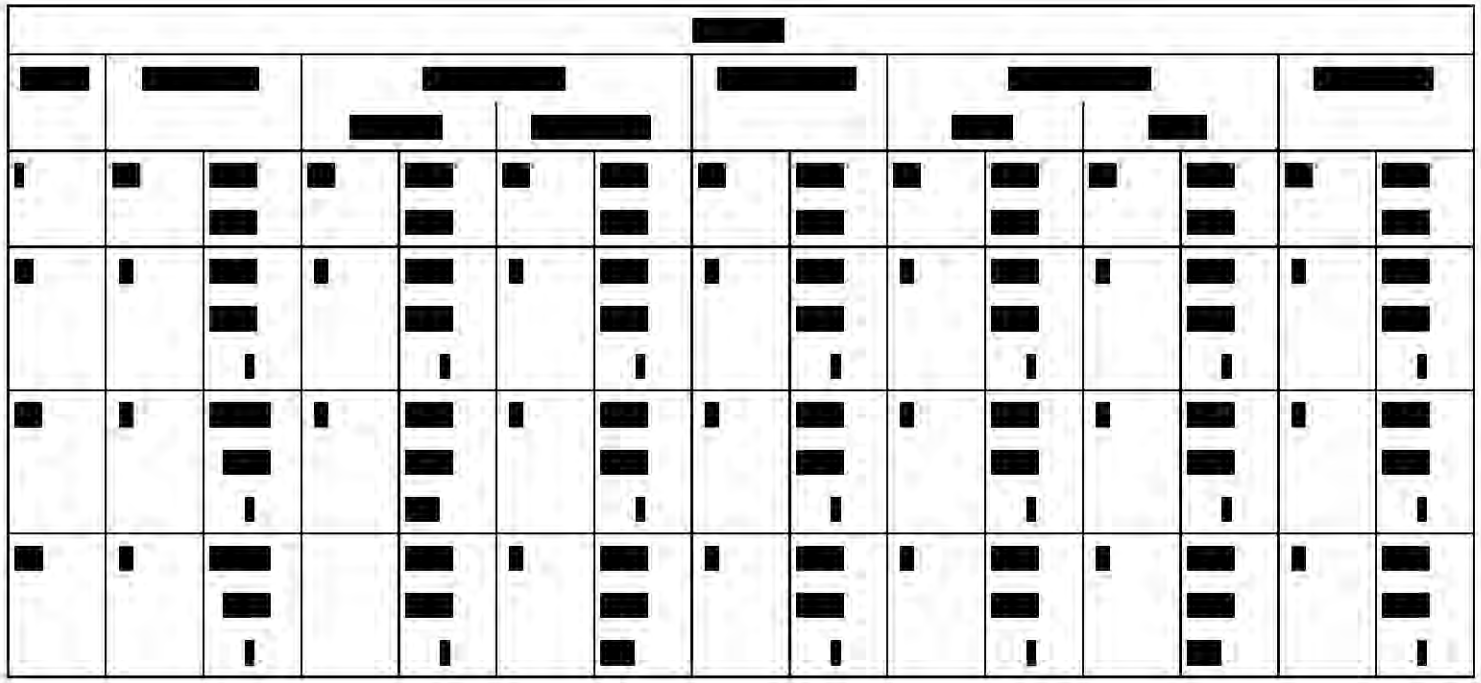

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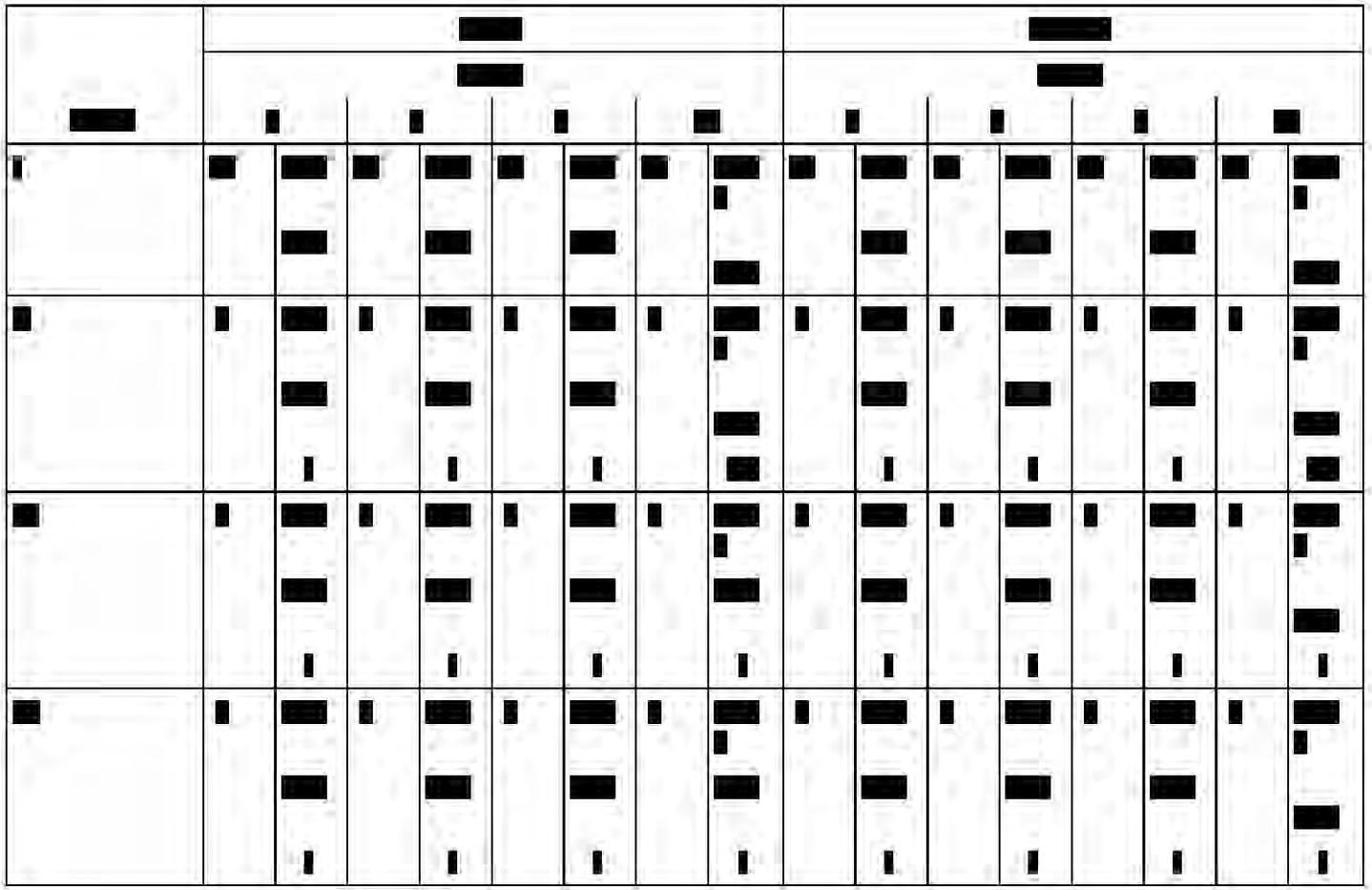

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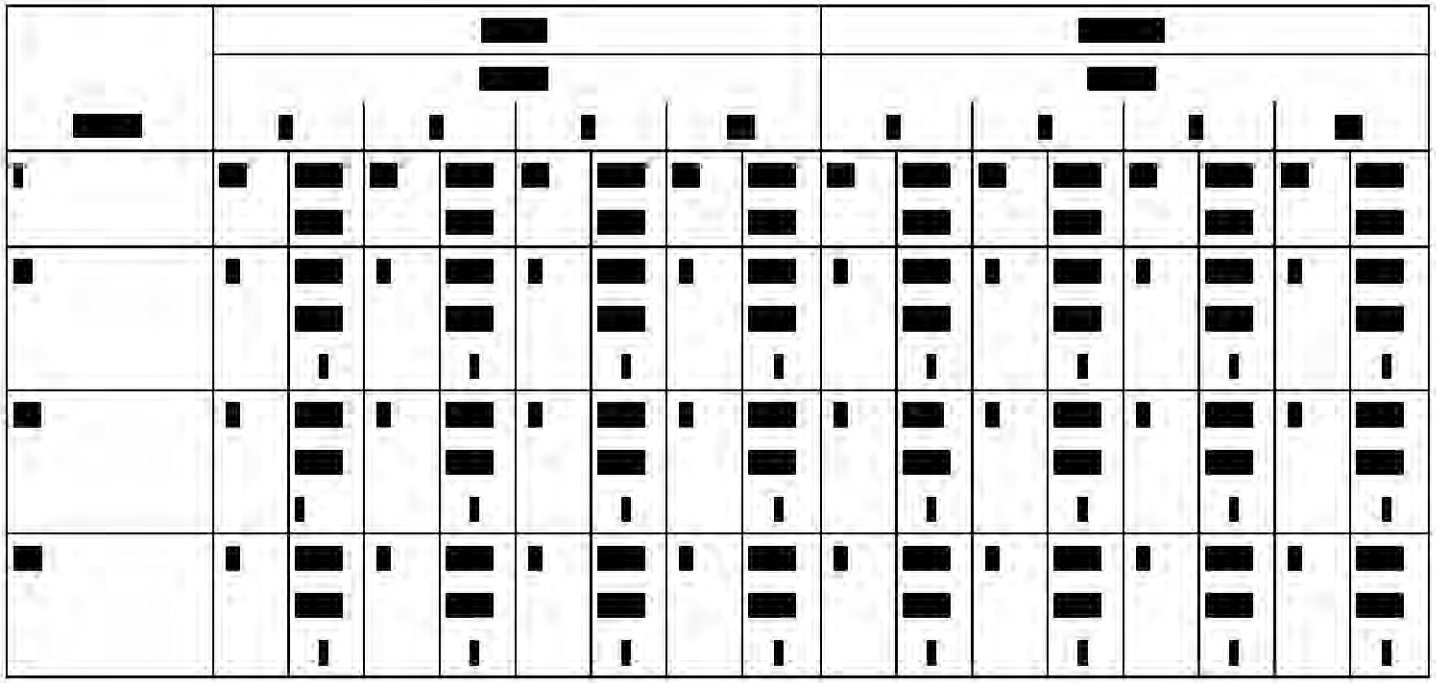

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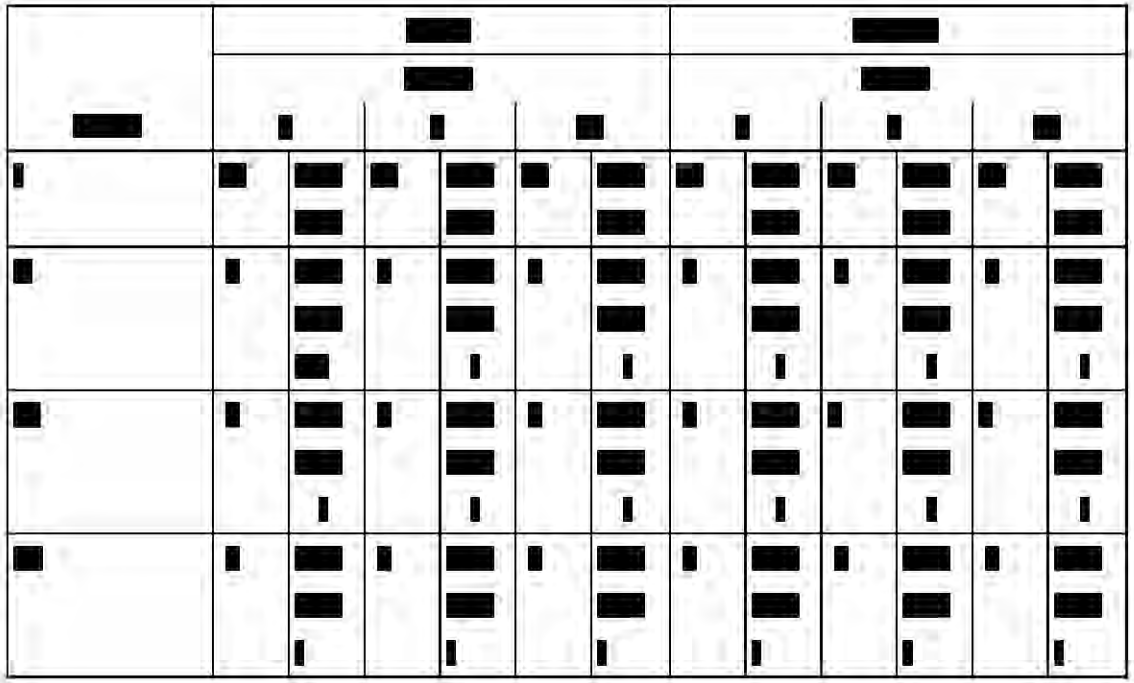

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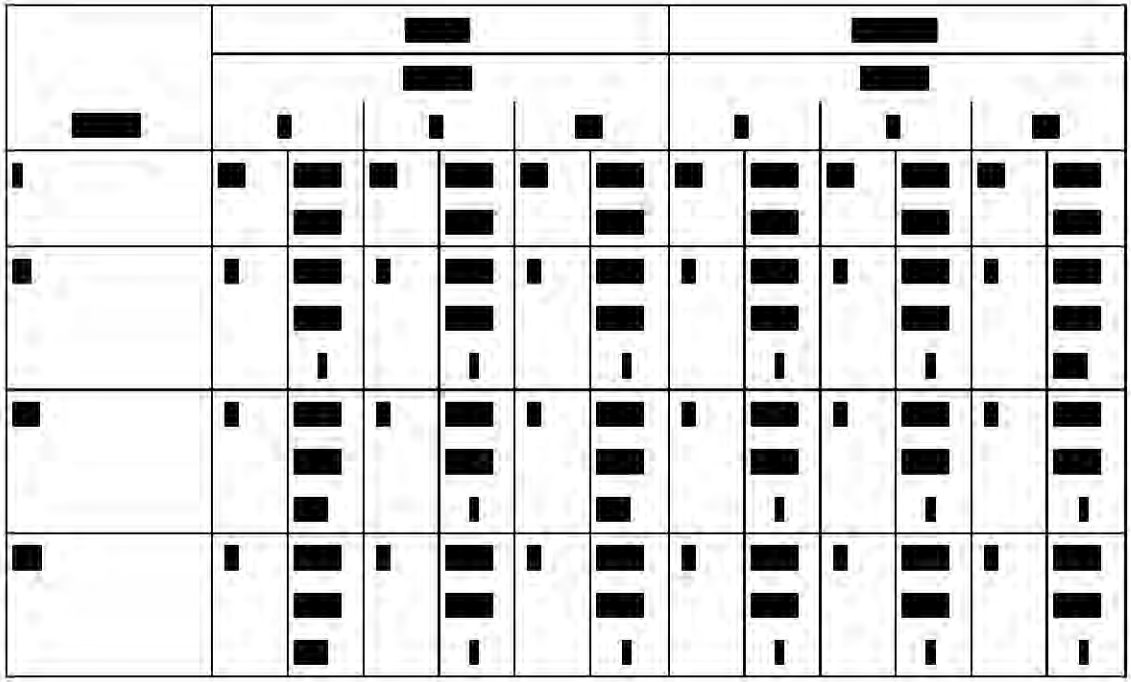

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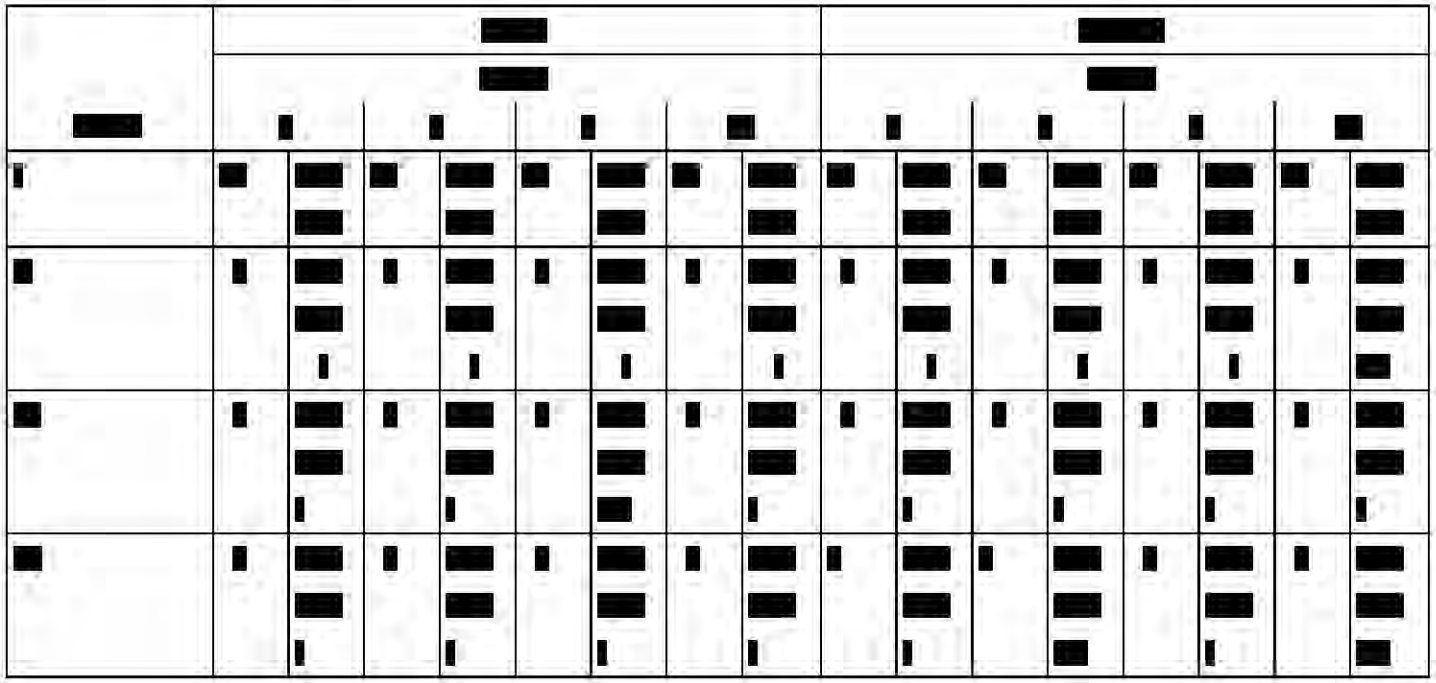

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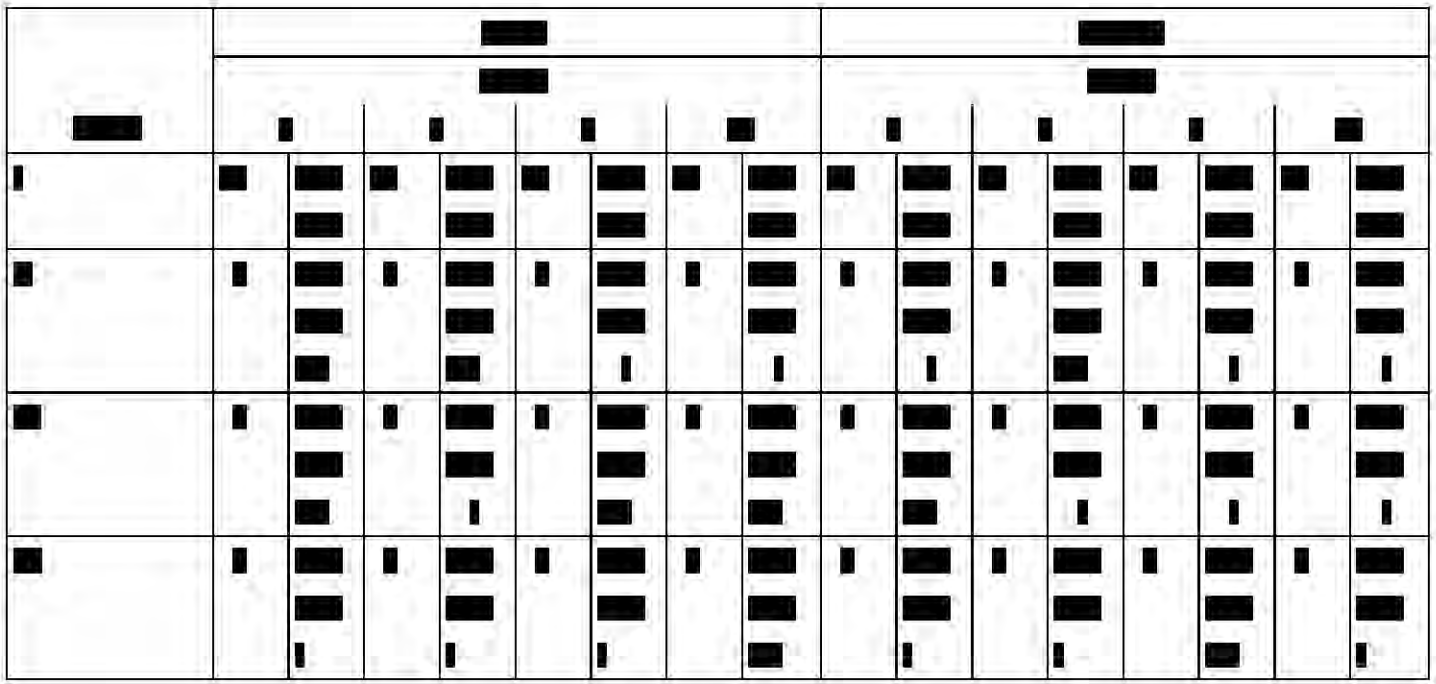

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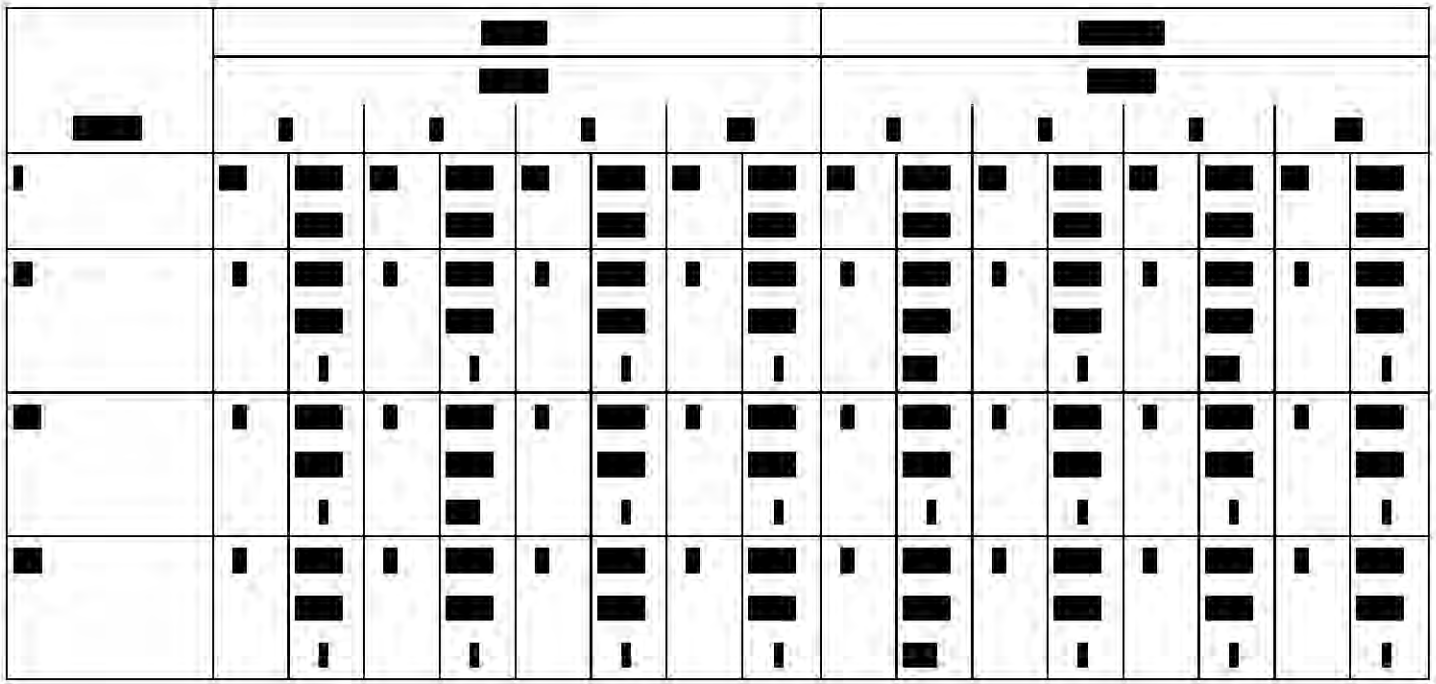

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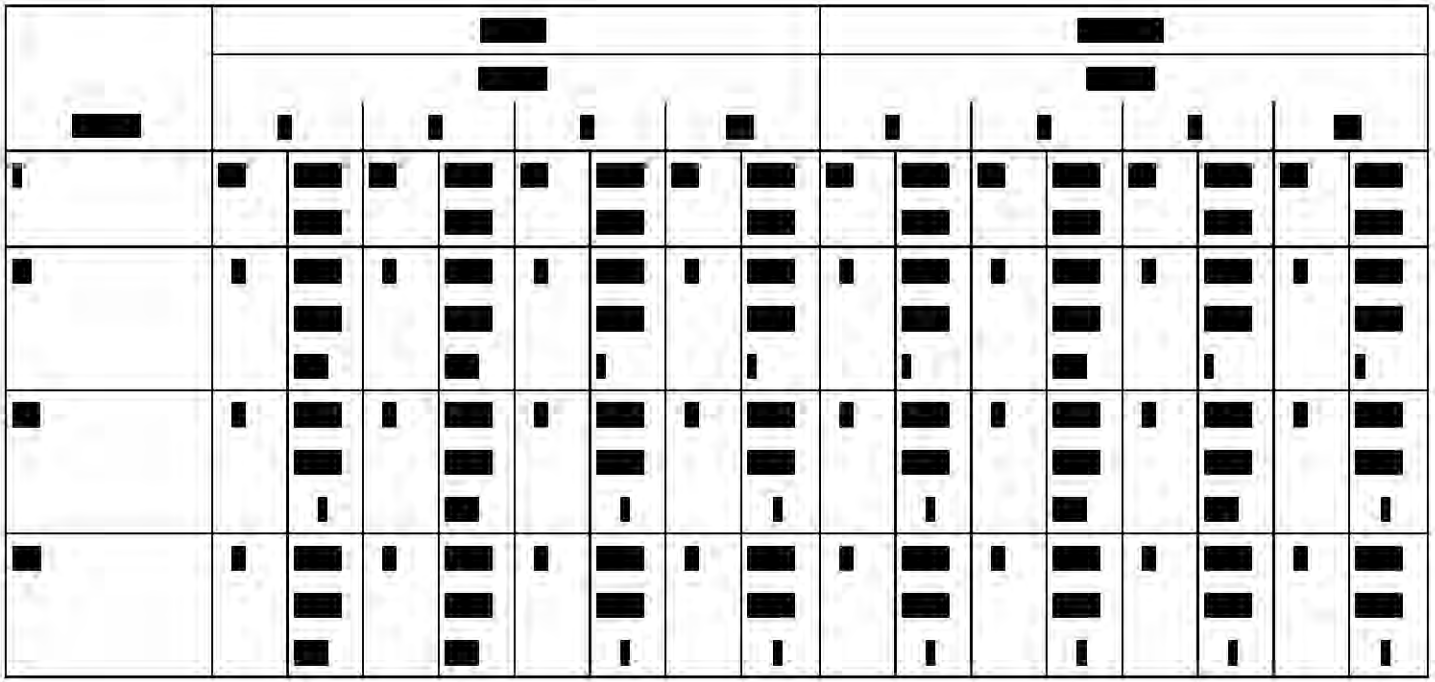

Section A6.4.1 Annex Point IIA VI 6.4	Subchronic oral toxicity test, non-rodent	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [X]	Technically not feasible [ ]	Scientifically unjustified [X]
Limited exposure [ ]	Other justification [ ]	

Detailed justification:

[redacted]

Section A6.4.1 Annex Point IIA VI 6.4	Subchronic oral toxicity test, non-rodent
Undertaking of intended data submission [ ]	
	Evaluation by Competent Authorities
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	[redacted]
Evaluation of applicant's justification	[redacted]
Conclusion	[redacted]
Remarks	
	COMMENTS FROM OTHER MEMBER STATE *(specify)*
Date	*Give date of comments submitted*
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table 4-2: Standard form for justification of the non-submission of data

Section A6.4.2 **Annex Point IIA6.4**	**Subchronic toxicity (dermal)**	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [X]	**Technically not feasible [ ]** **Scientifically unjustified [X]**	
Limited exposure [ ]	**Other justification [ ]**	
Detailed justification:		
Undertaking of intended data submission [ ]		
	Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	[redacted]	
Evaluation of applicant's justification	[redacted]	
Conclusion	[redacted]	
Remarks		
	COMMENTS FROM OTHER MEMBER STATE *(specify)*	
Date	*Give date of comments submitted*	
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*	
Conclusion	*Discuss if deviating from view of rapporteur member state*	
Remarks		

Section A6.3 / 6.4 / 6.5 Repeated dose toxicity

Annex Point IIA6.4.3 *(Subchronic inhalation toxicity test)*

Official use only

1 REFERENCE

1.1 Reference [redacted] A THIRTEEN WEEK INHALATION TOXICITY STUDY OF PHOSPHINE (PH_3) IN THE RAT, [redacted]

1.2 Data protection [redacted]

1.2.1 Data owner: Detia Freyberg GmbH

1.2.3 Criteria for data protection: [redacted]

2. GUIDELINES AND QUALITY ASSURANCE

2.1 Guideline study [redacted]

2.2 GLP [redacted]

2.3 Deviations [redacted]

3. MATERIALS AND METHODS

3.1 Test material [redacted]

3.1.1 Lot/Batch number: [redacted]

3.1.2 Specification: [redacted]

3.1.2.2 Purity: [redacted]

3.2 – 3.5 [redacted]

Section A6.3 / 6.4 / 6.5 Repeated dose toxicity

Annex Point IIA6.4.3 *(Subchronic inhalation toxicity test)*

[redacted]

4 RESULTS AND DISCUSSION

Three 6-hour exposures to 10 ppm phosphine were fatal to female rats. All other haematology, clinical chemistry, body weight and food consumption effects seen at this and lower exposure levels were completely reversible either during the exposure period or after a four week recovery period.

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods [redacted]

5.2 Results and discussion [redacted]

5.3 Conclusion

5.3.1 LO(A)EL [redacted]

5.3.2 NO(A)EL [redacted]

5.3.3 Reliability [redacted]

5.3.4 Deficiencies [redacted]

Section A6.3 / 6.4 / 6.5 Repeated dose toxicity

Annex Point IIA6.4.3 *(Subchronic inhalation toxicity test)*

	Evaluation by Competent Authorities
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	[redacted]
Materials and methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Results and discussion	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.4.3 Annex Point IIA VI 6.4	Subchronic inhalation toxicity test, non-rodent	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [X]	Technically not feasible [ ]	Scientifically unjustified [X]
Limited exposure [ ]	Other justification [ ]	

Detailed justification:

[redacted]

Undertaking of intended data submission [ ]

Section A6.4.3 Annex Point IIA VI 6.4	Subchronic inhalation toxicity test, non-rodent
	Evaluation by Competent Authorities
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	[redacted]
Evaluation of applicant's justification	[redacted]

Section A6.4.3 Annex Point IIA VI 6.4	Subchronic inhalation toxicity test, non-rodent
	[redacted]
Conclusion	[redacted]
Remarks	
	COMMENTS FROM OTHER MEMBER STATE *(specify)*
Date	*Give date of comments submitted*
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.3 / 6.4 / 6.5 Repeated dose toxicity

Annex Point IIA6.5/01 *Chronic toxicity (inhalation)*

Official use only

1 REFERENCE

1.1	**Reference**	[redacted] 2-YEAR COMBINED INHALATION CHRONIC TOXICITY AND ONCOGENICITY STUDY OF PHOSPHINE IN RATS, [redacted]
1.2	**Data protection**	[redacted]
1.2.1	Data owner	Detia Freyberg GmbH
1.2.2		
1.2.3	Criteria for data protection	[redacted]

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	[redacted]
2.2	**GLP**	[redacted]
2.3	**Deviations**	[redacted]

3 MATERIALS AND METHODS

3.1	**Test material**	[redacted]
3.1.1	Lot/Batch number	[redacted]
3.1.2	Specification	[redacted]
3.1.2.1	Description	[redacted]
3.1.2.2	Purity	[redacted]
3.1.2.3	Stability	[redacted]
3.2	**Test Animals**	
3.2.1	Species	[redacted]
3.2.2	Strain	[redacted]
3.2.3	Source	[redacted]
3.2.4	Sex	[redacted]
3.2.5	Age/weight at study initiation	[redacted]
3.2.6	Number of animals per group	[redacted]
3.2.7	Control animals	[redacted]

Section A6.3 / 6.4 / 6.5 Repeated dose toxicity

Annex Point IIA6.5/01 *Chronic toxicity (inhalation)*

3.3	**Administration/ Exposure**	[redacted]
3.3.1	Duration of treatment	[redacted]
3.3.2	Frequency of exposure	[redacted]
3.3.3	Postexposure period	[redacted]
3.3.4	**Oral**	
3.3.4.1	Type	[redacted]
3.3.4.2	Concentration	[redacted]
3.3.4.3	Vehicle	[redacted]
3.3.4.4	Concentration in vehicle	[redacted]
3.3.4.5	Total volume applied	[redacted]
3.3.4.6	Controls	[redacted]
3.3.5	**Inhalation**	
3.3.5.1	Concentrations	[redacted]
3.3.5.2	Particle size	[redacted]
3.3.5.3	Type or preparation of particles	[redacted]
3.3.5.4	Type of exposure	[redacted]
3.3.5.5	Vehicle	[redacted]
3.3.5.6	Concentration in vehicle	[redacted]
3.3.5.7	Duration of exposure	[redacted]
3.3.5.8	Controls	[redacted]

3.3.6 Dermal

3.3.6.1 Area covered [redacted]

3.3.6.2 Occlusion [redacted]

3.3.6.3 Vehicle [redacted]

3.3.6.4 Concentration in vehicle [redacted]

3.3.6.5 Total volume applied [redacted]

3.3.6.6 Duration of exposure [redacted]

3.3.6.7 Removal of test substance [redacted]

3.3.6.8 Controls [redacted]

3.3.7 Intraperitoneal/ Intravenous/ Intratracheal instillation

3.3.7.1 Vehicle [redacted]

3.3.7.2 Concentration in vehicle [redacted]

3.3.7.3 Total volume applied [redacted]

3.3.7.4 Controls [redacted]

3.4 Examinations

3.4.1 Observations

3.4.1.1 Clinical signs [redacted]

3.4.1.2 Mortality [redacted]

3.4.2 Body weight [redacted]

3.4.3 Food consumption [redacted]

3.4.4 Water consumption [redacted]

3.4.5 Ophthalmoscopic examination [redacted]

3.4.6 Haematology [redacted]

[redacted]

3.4.7 Clinical Chemisty

[redacted]

3.4.8 Urinalysis

[redacted]

3.5 Sacrifice and pathology

3.5.1 Organ Weights

[redacted]

3.5.2 Gross and histopathology

[redacted]

[redacted]

3.5.3 Other examinations [redacted]

3.5.4 Statistics [redacted]

[redacted]

3.6 Further remarks

4 RESULTS AND DISCUSSION

4.1 Observations

4.1.1 Clinical signs

Individual clinical signs and masses are presented in the original study report.

There was no apparent test article-related effect seen in the detailed clinical observations. The findings recorded occurred with a low incidence and were sporadic.

4.1.2 Mortality

A summary of mortality is presented in a table. A record of animal fate and disposition is presented in the original study report.

[redacted]

4.2 Body weight gain

[redacted]

4.3 Food consumption and compound intake

[redacted]

4.4 Ophtalmoscopic examination

[redacted]

4.5 Blood analysis

4.5.1 Haematology

[redacted]

4.5.2 Clinical chemistry

[redacted]

[redacted]

4.5.3 Urinalysis

[redacted]

4.6 Sacrifice and pathology

4.6.1 Organ weights

[redacted]

4.6.2 Gross and histopathology

[redacted]

[redacted]

[redacted]

4.7 Other

[redacted]

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

[redacted]

5.2 Results and discussion

[redacted]

5.3 Conclusion

5.3.1 LO(A)EL

[redacted]

5.3.2 NO(A)EL

[redacted]

5.3.3 Other

5.3.4 Reliability

[redacted]

5.3.5 Deficiencies

[redacted]

Evaluation by Competent Authorities

Use separate "evaluation boxes" to provide transparency as to the comments and views submitted

EVALUATION BY RAPPORTEUR MEMBER STATE

Date

Materials and Methods

Results and discussion

[redacted]

Conclusion

[redacted]

Reliability

[redacted]

Acceptability

[redacted]

Remarks

COMMENTS FROM ... *(specify)*

Date *Give date of comments submitted*

Materials and Methods *Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.*
Discuss if deviating from view of rapporteur member state

Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A6_3-1. Results of clinical chemistry haematology and urinalysis

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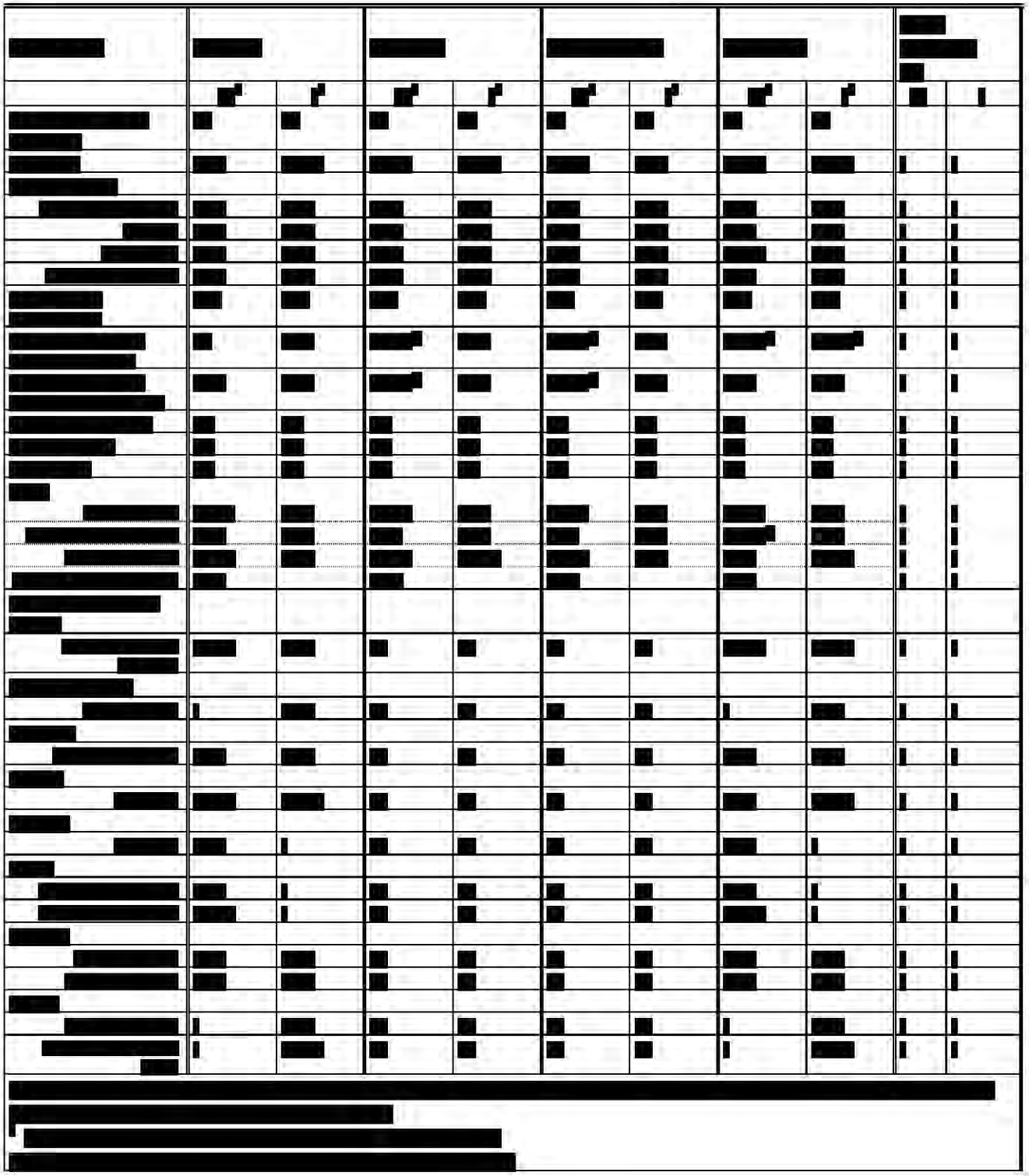

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Section A6.3 / 6.4 / 6.5 Repeated dose toxicity

Annex Point IIA VI.6.5/02 *Chronic toxicity*

Official use only

		1 REFERENCE
1.1	**Reference**	A.-M. Cabrol Telle et al (1985): NUTRITIONAL AND TOXICOLOGICAL EFFECTS OF LONG-TERM INGESTION OF PHOSPHINE-FUMIGATED DIET BY THE RAT, Fd. Chem. Toxic., Vol 23, No. 11, pp. 1001 – 1009, 1985
1.2	**Data protection**	No
1.2.1	Data owner	published
1.2.2		
1.2.3	Criteria for data protection	No data protection claimed
		2 GUIDELINES AND QUALITY ASSURANCE
2.1	**Guideline study**	No. (no guidelines available)
2.2	**GLP**	not stated
2.3	**Deviations**	n.a.
		3 MATERIALS AND METHODS
3.1	**Test material**	Phosphine released from aluminium phosphide.
3.1.1	Lot/Batch number	not stated
3.1.2	Specification	Deviating from specification given in section 2 as follows:
3.1.2.1	Description	The test diet was subjected to long-term fumigation with phosphine. The pellets were stored in bulk in sealed containers in which the level of fumigant was maintained at 2000 ppm. Sufficient quantities of diet were stored for periods of 6 months, so that over the 2-yr experiment the food received by the test animals had been fumigated for at least 6 months and had been maintained under phosphine until just before consumption, when it was aerated for 48 hr.
3.1.2.2	Purity	not stated
3.1.2.3	Stability	not stated
3.2	**Test Animals**	
3.2.1	Species	Rat
3.2.2	Strain	Sprague-Dawley
3.2.3	Source	not stated
3.2.4	Sex	60 males, 60 females
3.2.5	Age/weight at study initiation	Approximately 50 g
3.2.6	Number of animals per group	30 males and 30 females per group
3.2.7	Control animals	Yes

Section A6.3 / 6.4 / 6.5 Repeated dose toxicity

Annex Point IIA VI.6.5/02 *Chronic toxicity*

3.3	**Administration/ Exposure**	Oral
3.3.1	Duration of treatment	2 years
3.3.2	Frequency of exposure	daily (fumigated diet)
3.3.3	Postexposure period	not stated
3.3.4	**Oral**	
3.3.4.1	Type	in food
3.3.4.2	Concentration	The average residual level of phosphine was 5 ppb.
3.3.4.3	Vehicle	diet
3.3.4.4	Concentration in vehicle	5 ppb (see 3.3.4.2)
3.3.4.5	Total volume applied	not stated
3.3.4.6	Controls	plain diet, kept under identical conditions but without fumigation.
3.4	**Examinations**	
3.4.1	Observations	
3.4.1.1	Clinical signs	yes, daily
3.4.1.2	Mortality	yes, daily
3.4.2	Body weight	yes, each week during the first 3 months and than at longer intervals (every 2 or 3 week)
3.4.3	Food consumption	yes, each week during the first 3 months and than at longer intervals (every 2 or 3 week)
3.4.4	Water consumption	not stated
3.4.5	Ophthalmoscopic examination	not stated
3.4.6	Haematology	yes, number of animals: ten males, ten females time points: every three months Parameters: Haematocrit, erythrocyte count, total and differential leukocyte count
3.4.7	Clinical Chemisty	yes, number of animals: ten males, ten females time points: every three months Parameters: sodium, potassium, glucose, total cholesterol, urea, total bilirubin, creatinine, total protein, alkaline phosphatase, calcium chloride, carbonate phosphate, iron, uric acid, glutamic-pyruvic and glutamic-oxalacetic transaminase
3.4.8	Urinalysis	yes, number of animals: ten males, ten females time points: every three months Parameters: diuresis, pH, sodium, potassium, phosphorus, urea, creatinine, glutamic-oxalacetic transaminase, glucose ketones,

Section A6.3 / 6.4 / 6.5 Repeated dose toxicity

Annex Point IIA VI.6.5/02 *Chronic toxicity*

		urobilinogen, proteins, nitrite and blood.
3.5	**Sacrifice and pathology**	
3.5.1	Organ Weights	yes After 1 year of feeding, 19 male and 20 female controls and 20 male and 19 female treated rats were killed (one control and one treated rat having already died). The survivors of the remaining 40 animals were killed after 2 yr. At each time, the organs were weighed and examined macroscopically. Histology was carried out on the tissues in each group at 1 yr. Tumour frequency was recorded of all animals following the method of determination used by Fischer, Hutchinson, Berry et al. (1983). organs: parotid glands, stomach, caecum, liver, adrenals, gonads, thymus, lung, heart, spleen, kidney, brain
3.5.2	Gross and histopathology	yes After 1 year of feeding, 19 male and 20 female controls and 20 male and 19 female treated rats were killed (one control and one treated rat having already died). The survivors of the remaining 40 animals were killed after 2 yr. At each time, the organs were weighed and examined macroscopically. Histology was carried out on the tissues in each group at 1 yr. Tumour frequency was recorded of all animals following the method of determination used by Fischer, Hutchinson, Berry et al. (1983). organs: parotid glands, stomach, small intestine, colon, liver, adrenals, gonads, thyroid, thymus, lung, heart, carotid artery, spleen, kidney, muscle samples
3.5.3	Other examinations	no
3.5.4	Statistics	Student's-t-test
3.6	**Further remarks**	
		4 RESULTS AND DISCUSSION
4.1	**Observations**	
4.1.1	Clinical signs	No particular behavioural problems compared with those on the untreated diet.
4.1.2	Mortality	Apart from the one control and one treated rat that died in the first year, three control males, two treated males and one control female died by month and a further three male and two female controls, two treated males and two treated females by month 24.
4.2	**Body weight gain**	The growth curves show a very similar pattern of body-weight gain in the rats on the fumigated diet and the controls. For both sexes, the curves are superimposable up to about wk 8 of the study, when the body weights were slightly greater in the male controls than in the treated males. The reverse being true for the control and treated females. No significant differences persisted in the body weights.
4.3	**Food consumption and compound intake**	not stated

Section A6.3 / 6.4 / 6.5 Repeated dose toxicity

Annex Point IIA VI.6.5/02 *Chronic toxicity*

4.4	**Ophtalmoscopic examination**	no examination
4.5	**Blood analysis**	
4.5.1	Haematology	see table A6_5/02-1
4.5.2	Clinical chemistry	see table A6_5/02-2
4.5.3	Urinalysis	see table A6_5/02-3
4.6	**Sacrifice and pathology**	
4.6.1	Organ weights	The fresh weight of the organs taken from 20 rats of each group after 12 months on the diet did not show any significant differences between the control and treated groups when expressed relative to body weight, except in the case of the thymus, which was slightly heavier in the treated females than in the control group. (see table A6_5/02-4)
4.6.2	Gross and histopathology	Macroscopic examination on the various organs showed no anomalies either in the treated animals or in the controls. However, certain histopathological changes, notably congestion of the duodenum, ulcerous and necrotic zones in the colon and pigmentation indicating degeneration, were found more frequently in the treated animals. In all the other organs, changes of varying severity were observed in both control and treated animals. After 2 yrs in some organs histopathological changes were observed the colon of some treated animals showed ulceration or necrosis and a greater development of lymphoid tissue than in the controls, while zones of necrosis were seen to be more numerous in the duodenum of treated animals . All the organs, in both treated and control animals, showed signs of ageing, but these were particularly apparent in the spleen, kidneys, thymus, liver and adrenals. (see table A6_5/02-5)
4.7	**Other**	A certain number of tumours appeared in the rats killed at 2 yr, but the evaluation of tumour incidences did not show differences between treated and untreated rats.
		5 APPLICANT'S SUMMARY AND CONCLUSION
5.1	**Materials and methods**	Dietary toxicity study carried out over a period of 2 years.
5.2	**Results and discussion**	The results show that ingestion of a phosphine-fumigated diet by the rat for 2 years does not cause any marked modification of growth, food intake, nitrogen balance, body composition, functional behaviour or the incidence or type of tumours.
5.3	**Conclusion**	
5.3.1	LO(A)EL	not calculated
5.3.2	NO(A)EL	not calculated
5.3.3	Reliability	1
5.3.4	Deficiencies	No

Evaluation by Competent Authorities

EVALUATION BY RAPPORTEUR MEMBER STATE

Date	[redacted]
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	

COMMENTS FROM ... *(specify)*

Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A6_5/02-1. Results of clinical chemistry haematology and urinalysis

Haematological data for rats fed a phosphine-fumigated diet for up to 2 yr

Group	Erythrocytes (10^6/mm³)	Haematocrit (%)	Leucocytes: Total (10^3/mm³)	Differential* (%): N	E	L	M
Month 6							
Male							
Control	9.33 ± 0.19	49 ± 1.6	7.88 ± 0.50	19 ± 0.8	1 ± 0.3	74 ± 1.2	6 ± 0.3
Treated	9.69 ± 0.21	52 ± 0.8	8.98 ± 0.99	19 ± 0.8	3 ± 0.6	74 ± 1.4	5 ± 0.3
Female							
Control	8.23 ± 0.12	49 ± 0.9	5.42 ± 0.36	22 ± 1.3	2 ± 0.5	70 ± 1.6	5 ± 0.5
Treated	8.25 ± 0.20	48 ± 1.1	6.74 ± 0.57	18± 0.9	2± 0.6	74 ± 1.3	6 ± 0.3*
Month 12							
Male							
Control	8.75 ± 0.35	49 ± 1.0	13.55 ± 1.38	21 ± 0.6	0 ± 0.3	76 ± 0.4	3 ± 0.7
Treated	7.64 ± 0.23	45 ± 0.9	9.80 ± 1.22	22 ± 0.8	0 ± 0.2	72 ± 1.7	3 ± 0.7
Female							
Control	8.82 ± 0.25	47 ± 0.7	10.49 ± 2.0	24 ± 2.6	1 ± 0.4	76 ± 1.0	3 ± 0.4
Treated	8.00 ± 0.24	46 ± 0.6	11.27 ± 1.77	23 ± 1.1	1 ± 0.3	73 ± 2.7*	4 ± 0.4
Month 20							
Male							
Control	8.01 ± 0.55	49 ± 1.3	13.3 ± 0.64				
Treated	8.97 ± 0.91	48 ± 1.7	9.3 ± 0.32				
Female							
Control	7.45 ± 0.77	47 ± 1.6	3.6 ± 0.35				
Treated	8.97 ± 0.90	47 ± 0.8	3.5 ± 0.73				
Month 24							
Male							
Control	5.79 ± 0.65	44 ± 1.6	6.0 ± 0.18	30 ± 1.2	0 ± 0.2	66 ± 1.3	4 ± 0.4
Treated	6.70 ± 0.49	45 ± 1.3	10.7 ± 0.41	30 ± 1.2	1 ± 0.3	65 ± 1.1	4 ± 0.4
Female							
Control	5.43 ± 0.56	45 ± 0.8	5.7 ± 0.24	26 ± 1.4	1 ± 0.2	68 ± 1.5	5 ± 0.4
Treated	6.33 ± 0.60	45 ± 1.2	10.8 ± 0.32	30 ± 1.7**	1 ± 0.3	62 ± 1.8**	4 ± 0.5

N = Neutrophils, E = Eosinophils, L = Lymphocytes, M = Monocyte

*No basophils were found in any of these differential counts.

Values are means ± SEM for groups of ten rats. Those marked with asterisks differ significantly (by student's t test) from the corresponding control value: * $p < 0,05$; ** $p < 0,01$

Table A6_5/02-2. Results of repeated dose toxicity study

Plasma analysis data for rats fed a phosphine fumigated diet for up to 2 yr.

Plasma component	Values for samples taken at month:							
	3		6		12		24	
	Control group	Treated group	Control group	Treated group	Control group	Treated group	Control group	Treated group
	male							
Urea (mM)	6.01 ± 0.13	6.05 ± 0.31	5.87 ± 0.28	5.47 ± 0.28	6.35 ± 0.26	6.37 ± 0.21	5.71 ± 0.31	5.98 ± 0.75
Creatinine (µM)	46 ± 2.1	45 ± 1.5	39 ± 2.4	45 ± 2.2	53 ± 1.6	45 ± 1.1***	49 ± 3.2	57 ± 6.6
Calcium (mM)	2.67 ± 0.03	2.07 ± 0.32	2.62 ± 0.02	2.66 ± 0.04	2.57 ± 0.03	2.56 ± 0.03	2.61 ± 0.06	2.62 ± 0.06
Phosphate (mM)	2.20 ± 0.06	2.10 ± 0.06	1.65 ± 0.06	1.66 ± 0.09	1.41 ± 0.05	1.53 ± 0.10	1.85 ± 0.13	1.84 ± 0.31
Alk. Pase (U/litre)	255 ± 26.9	293 ± 27.6	182 ± 24.0	181 ± 15.0	141 ± 22.9	129 ± 14.3	97 ± 12.0	105 ± 19.8
Total bilirubin (µM)	2.0 ± 0.00	2.0 ± 0.20	2.0 ± 0.10	2.0 ± 0.10	2.0 ± 0.20	1.0 ± 0.20	2.0 ± 0.20	2.0 ± 0.20
GPT (U/litre)	92 ± 8.2	88 ± 9.2	143 ± 4.5	136 ± 1.7	198 ± 51.8	182 ± 52.8	172 ± 40.6	128 ± 49.4
GOT (U/litre)	52 ± 3.2	49 ± 3.3	70 ± 2.0	65 ± 1.7	245 ± 52.6	218 ± 70.7	284 ± 100	196 ± 124
Uric acid (µM)	28 ± 2.9	28 ± 2.7	21 ± 2.5	20 ± 2.5	13 ± 1.7	19 ± 3.0	23 ± 6.9	37 ± 16.4
Cholesterol (mM)	2.71 ± 0.18	2.87 ± 0.13	3.15 ± 0.13	3.22 ± 0.12	3.33 ± 0.11	3.56 ± 0.16	4.66 ± 0.57	4.01 ± 0.27
Glucose (mM)	7.83 ± 0.28	7.93 ± 0.24	6.32 ± 0.20	6.67 ± 0.18	9.98 ± 0.31	10.55 ± 1.06	9.59 ± 0.78	12.42 ± 2.61

Alk. Pase = Alkaline phosphatase; GPT = Glutamic-pyruvic transaminase; GOT = Glutamic-oxalacetic transaminase

Values are means ± SEM for groups of ten rats. Those marked with asterisks differ significantly (by student's t test) from the corresponding control value: * $p < 0,05$; ** $p < 0,01$; *** $p<0.001$.

Plasma component	Values for samples taken at month:							
	3		6		12		24	
	Control	Treated	Control	Treated	Control	Treated	Control	Treated
	female							
Urea (mM)	5.8 ± 0.17	5.92 ± 0.18	6.18 ± 0.32	5.88 ± 0.18	5.41 ± 0.44	5.57 ± 0.50	6.11 ± 0.65	8.20 ± 2.73
Creatinine (µM)	47 ± 1.3	51 ± 2.3	40 ± 3.8	43 ± 1.9	56 ± 2.4	46 ± 1.7**	67 ± 8.5	70 ± 15.4
Calcium (mM)	2.69 ± 0.05	2.78 ± 0.02	2.72 ± 0.03	2.73 ± 0.03	2.67 ± 0.06	2.57 ± 0.04	2.69 ± 0.10	2.66 ± 0.07
Phosphate (mM)	2.47 ± 0.10	2.41 ± 0.11	1.76 ± 0.03	1.74 ± 0.07	1.69 ± 0.03	1.67 ± 0.08	1.84 ± 0.45	2.09 ± 0.28
Alk. Pase (U/litre)	265 ± 32.7	329 ± 29.4	188 ± 16.6	232 ± 23.5	122 ± 24.8	114 ± 10.7	116 ± 12.2	124 ± 24.7
Total bilirubin (µM)	2.0 ± 0.00	2.0 ± 0.00	2.0 ± 0.30	2.0 ± 0.20	1.0 ± 0.30	1.0 ± 0.20	1.0 ± 0.20	1.0 ± 0.20
GPT (U/litre)	83 ± 5.7	89 ± 9.2	55 ± 3.4	52 ± 3.0	63 ± 5.0	71 ± 13.0	87 ± 7.6	86 ± 17.7
GOT (U/litre)	55 ± 2.4	59 ± 8.5	58 ± 3.2	78 ± 10.1	79 ± 16.0	95 ± 16.0	123 ± 17.3	74 ± 18.5
Uric acid (µM)	37 ± 17.2	35 ± 4.2	18 ± 2.6	14 ± 2.2	16 ± 2.2	15 ± 3.3	56 ± 18.9	65 ± 22.4
Cholesterol (mM)	2.43 ± 0.04	2.63 ± 0.05**	3.12 ± 0.08	3.74 ± 0.16*	3.79 ± 0.24	4.03 ± 0.32	6.11 ± 0.65	5.81 ± 0.44
Glucose (mM)	7.96 ± 0.17	7.95 ± 0.30	7.52 ± 0.17	6.99 ± 0.29	9.11 ± 0.32	9.76 ± 0.52	11.55 ± 1.00	11.52 ± 0.86

Alk. Pase = Alkaline phosphatase; GPT = Glutamic-pyruvic transaminase; GOT = Glutamic-oxalacetic transaminase

Values are means ± SEM for groups of ten rats. Those marked with asterisks differ significantly (by student's t test) from the corresponding control value: * $p < 0,05$; ** $p < 0,01$; *** $p<0.001$.

Table A6_5/02-3. Analysis of urine samples from rats fed a phosphine-fumigated diet for up to 2 yr

Group	Phosphorus (g 24 hr)	Urea (g 24 hr)	Creatinine (mg 24 hr)	GOT (U/litre)	Diuresis (ml 24 hr)	pH
Month 3						
Male						
Control	0.026 ± 0.034	0.67 ± 0.19	28.60 ± 10.5	7 ± 2.0	17.8 ± 5.28	7.3 ± 0.4
Treated	0.032 ± 0.0038	0.71 ± 0.19	21.62 ± 7.70	8 ± 1.2	12.3 ± 3.37	7 ± 0.3
Female						
Control	0.027 ± 0.0038	0.61 ± 0.15	16.08 ± 3.56	8 ± 4.1	15 ± 1.8	7 ± 0.2
Treated	0.034 ± 0.0048	0.52 ± 0.2	14.65 ± 4.71	7 ± 2.3	14 ± 2.8	7.3 ± 0.4
Month 6						
Male						
Control	0.016 ± 0.0022	0.45 ± 0.075	9.51 ± 1.44	7 ± 0.9	14 ± 3.4	7.8 ± 0.46
Treated	0.017 ± 0.0026	0.49 ± 0.052	8.96 ± 1.94	6 ± 1.0	11 ± 2.8	6.9 ± 0.45
Female						
Control	0.019 ± 0.0033	0.51 ± 0.061	14.63 ± 1.56	8 ± 1.5	10 ± 1.1	8 ± 0.5
Treated	0.016 ± 0.0024	0.45 ± 0.066	14.89 ± 2.52	9 ± 1.2	9 ± 2.1	6.9 ± 0.45
Month 10						
Male						
Control	0.017 ± 0.0033	0.42 ± 0.031	9.5 ± 1.15	4.8 ± 0.87	9 ± 1.2	5.8 ± 0.48
Treated	0.019 ± 0.0037	0.45 ± 0.049	7.1 ± 1.89	3.7 ± 1.25	10 ± 1.1	6.4 ± 0.20
Female						
Control	0.024 ± 0.00	0.52 ± 0.067	16.3 ± 2.0	6.92 ± 1.29	14 ± 2.2	6.9 ± 0.08
Treated	0.028 ± 0.002	0.52 ± 0.057	20.2 ± 2.45	5.13 ± 1.49	11 ± 1.4	6.9 ± 0.17
Month 12						
Male						
Control	0.018 ± 0.003	0.55 ± 0.18	14 ± 3.8		15 ± 2.7	7 ± 0.2
Treated	0.015 ± 0.0025	0.76 ± 0.15	15 ± 2.4		14 ± 2.4	7 ± 0.2
Female						
Control	0.025± 0.0031	0.70 ± 0.14	16 ± 3.7		20 ± 2.9	7 ± 0.3
Treated	0.029 ± 0.0053	0.89 ± 0.13	18.2 ± 2.93		17 ± 2.3	7 ± 0.2
Month 18						
Male						
Control	0.031 ± 0.005	0.66 ± 0.084	2.04 ± 0.2	3 ± 0.4	15 ± 2.3	7 ± 0.4
Treated	0.025 ± 0.004	0.56 ± 0.069	1.64 ± 0.14	5 ± 0.6	19 ± 1.8	7 ± 0.3
Female						
Control	0.039 ± 0.008	0.79 ± 0.053	17.72 ± 1.86	8 ± 1.4	20 ± 2.0	7 ± 0.2

	Treated	0.033 ± 0.006	0.81 ± 0.19	20.33 ± 2.04	3 ± 0.5**	21 ± 2.8	8 ± 0.4
Month 21							
Male							
	Control	0.031 ± 0.0053	0.57 ± 0.144	13.2 ± 1.39	5 ± 0.5	22 ± 3.1	7 ± 0.2
	Treated	0.030 ± 0.0079	0.69 ± 0.049	15.49 ± 0.82	3 ± 0.7	26 ± 2.2	7 ± 0
Female							
	Control	0.038 ± 0.0043	0.64 ± 0.102	19.65 ± 2.64	1 ± 0	31 ± 8.3	7 ± 0.2
	Treated	0.037 ± 0.0049	1.31 ± 0.54	21.89 ± 3.69	3 ± 0.8	28 ± 6.4	7 ± 0.2
Month 24							
Male							
	Control	0.030 ± 0.0057	0.87 ± 0.1487	14.8 ± 1.45	4 ± 0.5	20 ± 3.8	7 ± 0.2
	Treated	0.031 ± 0.0045	0.73 ± 0.060	16.72 ± 0.76	3 ± 0.5	27 ± 3.7	6 ± 0.2
Female							
	Control	0.035 ± 0.0069	0.84 ± 0.143	22.7 ± 2.36	2 ± 0.4	18 ± 2.5	7 ± 0
	Treated	0.040 ± 0.0057	1.19 ± 0.30	23.99 ± 2.06	4 ± 0.9	20 ± 4.7	6.7 ± 0.15

GOT = Glutamic-oxalacetic transaminase

Values are means ± SEM for groups of ten rats. Those marked with asterisks differ significantly (by student's t test) from the corresponding control value: * $p < 0,05$; ** $p < 0,01$

Table A6_5/02-4. Fresh (relative) weight of organs from rats fed a phosphine-fumigated diet for up to 2 yr

	Organ weights (g/100g body weight) after treatment for 2yr			
	Males		females	
Organ	Control	Treated	Control	Treated
Parotid gland	0.16 ± 0.06	0.18 ± 0.008	0.28 ± 0.091	0.19 ± 0.013
Stomach	0.53 ± 0.020	0.58 ± 0.055	0.60 ± 0.012	0.57 ± 0.032
Liver	3.74 ± 0.36	3.34 ± 0.26	3.27 ± 0.106	2.97 ± 0.201
Adrenals	0.012 ± 0.001	0.016 ± 0.001	0.018 ± 0.001	0.021 ± 0.001
Gonad	0.82 ± 0.081	0.85 ± 0.06	0.09 ± 0.008	0.09 ± 0.010
Thymus	0.11 ± 0.06	0.20 ± 0.081	0.10 ± 0.010	0.13 ± 0.010*
Lung	0.43 ± 0.08	0.44 ± 0.017	0.48 ± 0.015	0.41 ± 0.016**
Heart	0.37 ± 0.024	0.39 ± 0.054	0.38 ± 0.018	0.36 ± 0.020
Spleen	0.19 ± 0.027	0.20 ± 0.012	0.20 ± 0.022	0.16 ± 0.006
Kidney	0.80 ± 0.089	0.84 ± 0.075	1.37 ± 0.038	1.16 ± 0.010

Values are means ± SEM for groups of approximately 10 rats after 2 yr. Those marked with asterisks differ significantly (by student's t test) from the corresponding control value: * $p < 0,05$; ** $p < 0,01$

Table A6_5/02-5.

Tissue and lesion	No. of rats with lesion after 2 yr.			
	Males		females	
	Control	Treated	Control	Treated
Duodenum *No. examined...*	6	10	9	10
Ulcerous zones	0	0	0	0
Increased lymphoid tissue	5	10	9	9
Congestion	0	0	0	0
Necrotic zones	1	3	0	2
Colon *No. examined...*	7	10	10	9
Ulcerous or necrotic zones	0	2	0	0
Inflamed zones	0	0	0	0
Epithelial desquamation	0	0	0	0
Increased lymphoid tissue	0	2	0	1

Section A6.3 / 6.4 / 6.5 Repeated dose toxicity

Annex Point IIA VI.6.5/03 *Chronic toxicity*

Official use only

	1 REFERENCE	
1.1	**Reference**	[redacted] 2 years toxicity studies with PHOSTOXIN-treated food on rats, [redacted]
1.2	**Data protection**	[redacted]
1.2.1	Data owner	Detia Freyberg GmbH
1.2.2		
1.2.3	Criteria for data protection	[redacted]
	2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	[redacted]
		[redacted]
2.2	**GLP**	[redacted]
		[redacted]
2.3	**Deviations**	[redacted]
	3 MATERIALS AND METHODS	
3.1	**Test material**	[redacted]
3.1.1	Lot/Batch number	[redacted]
3.1.2	Specification	[redacted]
3.1.2.1	Description	[redacted]
3.1.2.2	Purity	[redacted]
3.1.2.3	Stability	[redacted]
3.2	**Test Animals**	
3.2.1	Species	[redacted]
3.2.2	Strain	[redacted]
3.2.3	Source	[redacted]
3.2.4	Sex	[redacted]
3.2.5	Age/weight at study initiation	[redacted]
3.2.6	Number of animals per group	[redacted]
3.2.7	Control animals	[redacted]
3.3	**Administration/ Exposure**	[redacted]
3.3.1	Duration of treatment	[redacted]

Section A6.3 / 6.4 / 6.5 Repeated dose toxicity

Annex Point IIA VI.6.5/03 *Chronic toxicity*

3.3.2	Frequency of exposure	[redacted]
3.3.3	Postexposure period	[redacted]
3.3.4	**Oral**	
3.3.4.1	Type	[redacted]
3.3.4.2	Concentration	[redacted]
3.3.4.3	Vehicle	[redacted]
3.3.4.4	Concentration in vehicle	[redacted]
3.3.4.5	Total volume applied	[redacted]
3.3.4.6	Controls	[redacted]
3.4	**Examinations**	
3.4.1	Observations	
3.4.1.1	Clinical signs	[redacted]
3.4.1.2	Mortality	[redacted]
3.4.2	Body weight	[redacted]
3.4.3	Food consumption	[redacted]
3.4.4	Water consumption	[redacted]
3.4.5	Ophthalmoscopic examination	[redacted]
3.4.6	Haematology	[redacted]
3.4.7	Clinical Chemisty	[redacted]
3.4.8	Urinalysis	[redacted]
3.5	**Sacrifice and pathology**	

Section A6.3 / 6.4 / 6.5 Repeated dose toxicity

Annex Point IIA VI.6.5/03 *Chronic toxicity*

3.5.1 Organ Weights [redacted]

3.5.2 Gross and histopathology [redacted]

3.5.3 Other examinations [redacted]

3.5.4 Statistics [redacted]

3.6 Further remarks [redacted]

4 RESULTS AND DISCUSSION

4.1 Observations

4.1.1 Clinical signs [redacted]

4.1.2 Mortality [redacted]

4.2 Body weight gain [redacted]

4.3 Food consumption and compound intake [redacted]

4.4 Ophtalmoscopic examination

4.5 Blood analysis

4.5.1 Haematology [redacted]

4.5.2 Clinical chemistry [redacted]

4.5.3 Urinalysis [redacted]

4.6 Sacrifice and pathology

4.6.1 Organ weights [redacted]

Section A6.3 / 6.4 / 6.5 Repeated dose toxicity

Annex Point IIA VI.6.5/03 *Chronic toxicity*

4.6.2 Gross and histopathology

[redacted]

4.7 Other

[redacted]

Section A6.3 / 6.4 / 6.5 Repeated dose toxicity

Annex Point IIA VI.6.5/03 *Chronic toxicity*

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	[redacted]
5.2	**Results and discussion**	Feeding of male and female Wistar rats with Phostoxin-fumigated diet (phosphine level: 0.167 – 0.377 mg/kg the first 16 weeks, 0.996 mg/kg week 17 – 104) did not reveal any toxic effects in this 2 year dietary feeding study.
5.3	**Conclusion**	
5.3.1	LO(A)EL	[redacted]
5.3.2	NO(A)EL	[redacted]
5.3.3	Other	[redacted]
5.3.4	Reliability	[redacted]
5.3.5	Deficiencies	[redacted]

Evaluation by Competent Authorities

EVALUATION BY RAPPORTEUR MEMBER STATE

Date	[redacted]
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]

COMMENTS FROM ... *(specify)*

Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*

Section A6.3 / 6.4 / 6.5 Repeated dose toxicity

Annex Point IIA VI.6.5/03 *Chronic toxicity*

Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A6_3-1. Results of clinical chemistry haematology and urinalysis

(Use this or similar table, if relevant effects occur and if time sequence is important.Give either symbols for increases or decreases (↑↓) or abbreviations inc., dec. Only if more information is needed, give figures or percentages.)

parameter changed	Unit	Controls			low dose			medium dose			high dose		
weeks after start of treatment													
males													
females													

* $p < 0,05$

Give only those parameters which are changed in at least one dose group compared to control. Usually only statistically significant effects

Depending on number of parameters changed one table each for Haematology, Clinical Chemistry, Urinalysis

Table A6_3-2. Results *(specify)* of repeated dose toxicity study

Parameter	Control		low dose		medium dose		high dose		dose-response +/-	
	m[a]	f[a]	m[a]	f[a]	m[a]	f[a]	m[a]	f[a]	m	f
number of animals examined										
Mortality										
clinical signs*										
body weight										
food consumption										
clinical chemistry*										
haematology*										
urinalysis*										
Organ x organ weight*										
gross pathology*										
microscopic pathology*										
Organ y										

* *specify effects; for different organs give special findings in the order organ weight, gross pathology and microscopic pathology if there are effects*

[a] *give number of animals affected/total number of animals, percentage, or just ↑ or ↓ for increased or decreased*

Section A6.6.1 Genotoxicity in vitro

Annex Pt IIA VI.6.6.1/01 *In-vitro gene mutation study in bacteria*

Official use only

1 REFERENCE

1.1 Reference [redacted] IN VITRO MICROBIAL MUTAGENICITY TESTING OF HYDROGEN PHOSHIDE, [redacted]

1.2 Data protection [redacted]

1.2.1 Data owner: Detia Freyberg GmbH

1.2.2

1.2.3 Criteria for data protection: [redacted]

2 GUIDELINES AND QUALITY ASSURANCE

2.1 Guideline study [redacted]

2.2 GLP [redacted]

2.3 Deviations [redacted]

3 MATERIALS AND METHODS

3.1 Test material [redacted]

3.1.1 Lot/Batch number: [redacted]

3.1.2 Specification: [redacted]

3.1.2.1 Description: [redacted]

3.1.2.2 Purity: [redacted]

3.1.2.3 Stability: [redacted]

3.2 Study Type [redacted]

3.2.1 Organism/cell type: [redacted]

3.2.2 Deficiencies / Proficiencies: [redacted]

3.2.3 Metabolic activation system: [redacted]

Section A6.6.1 Genotoxicity in vitro

Annex Pt IIA VI.6.6.1/01 *In-vitro gene mutation study in bacteria*

3.2.4	Positive control	[redacted]
3.3	**Administration / Exposure; Application of test substance**	
3.3.1	Concentrations	[redacted]
3.3.2	Way of application	[redacted]
3.3.3	Pre-incubation time	[redacted]
3.3.4	Other modifications	[redacted]
3.4	**Examinations**	[redacted]
3.4.1	Number of cells evaluated	[redacted]

4 RESULTS AND DISCUSSION

4.1	**Genotoxicity**	
4.1.1	without metabolic activation	No
4.1.2	with metabolic activation	No
4.2	**Cytotoxicity**	n. a.
4.3	**Further examinations**	In the toxicity test of hydrogen phosphide with Salmonella typhimurium TA 98, approximately 20% growth inhibition was observed at the highest concentration, but no toxic effect was observed at lower concentrations.

Section A6.6.1 Genotoxicity in vitro

Annex Pt IIA VI.6.6.1/01 *In-vitro gene mutation study in bacteria*

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	[redacted]
5.2	**Results and discussion**	[redacted]
5.3	**Conclusion**	
5.3.1	Reliability	[redacted]
5.3.2	Deficiencies	[redacted]

Evaluation by Competent Authorities

EVALUATION BY RAPPORTEUR MEMBER STATE

Date	[redacted]
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	[redacted]

COMMENTS FROM ...

Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.6.1 Genotoxicity in vitro

Annex Pt IIA VI.6.6.1/01 *In-vitro gene mutation study in bacteria*

Table A6_6_1-1.Table for Gene Mutation Assay (modify if necessary)

Concentration [µg/ml or other]	Number of mutant cells		Comments *give information on cytotoxicity or other*
	— S9	+ S9	
0			
x			
xx			

Table A6_6_1-2.Table for Cytogenetic In-Vitro-Test: Chromosomal Analysis (modify if necessary)

		control	**low dose**	**mid dose**	**high dose**
cytotoxicity *specify measure of cytotoxicity*		yes/no	yes/no	yes/no	yes/no
state mean and standard deviations below					
chromatid aberrations	gaps				
	breaks				
	interchanges				
Isochromatid aberrations	gaps				
	breaks				
	interchanges				
mitotic index					
polyploidy					
endo reduplication					

Section A6.6.1/6.6.2/ 6.6.3 Genotoxicity in vitro

Bacterial reverse mutation test

Annex Pt IIA VI.6.6.1/02

Official use only

1 REFERENCE

1.1	**Reference**	[redacted] Ames/Salmonella Plate Incorporation Assay on Hydrogen Phosphide (PH_3), [redacted]
1.1	**Data protection**	[redacted]
1.1.1	Data owner	Detia Freyberg GmbH
1.1.2		
1.1.3	Criteria for data protection	[redacted]

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	[redacted]
2.2	**GLP**	[redacted]
2.3	**Deviations**	[redacted]

3 MATERIALS AND METHODS

3.1	**Test material**	[redacted]
3.1.1	Lot/Batch number	[redacted]
3.1.2	Specification	[redacted]
3.1.2.1	Description	[redacted]
3.1.2.2	Purity	[redacted]
3.1.2.3	Stability	[redacted]
3.2	**Study Type**	[redacted]
3.2.1	Organism/cell type	[redacted]

Section A6.6.1/6.6.2/ 6.6.3

Genotoxicity in vitro

Bacterial reverse mutation test

Annex Pt IIA VI.6.6.1/02

3.2.2	Deficiencies / Proficiencies	[redacted]
3.2.3	Metabolic activation system	[redacted]
3.2.4	Positive control	[redacted]
3.3	**Administration / Exposure; Application of test substance**	[redacted]
3.3.1	Concentrations	[redacted]

Section A6.6.1/6.6.2/ 6.6.3 **Genotoxicity in vitro**

Bacterial reverse mutation test

Annex Pt IIA VI.6.6.1/02

3.3.2 Way of application [redacted]

3.3.3 Pre-incubation time [redacted]

3.3.4 Other modifications [redacted]

3.4 Examinations [redacted]

3.4.1 Number of cells evaluated [redacted]

4 RESULTS AND DISCUSSION

4.1 Genotoxicity

Section A6.6.1/6.6.2/ 6.6.3 Genotoxicity in vitro

Bacterial reverse mutation test

Annex Pt IIA VI.6.6.1/02

4.1.1 without metabolic activation

[redacted]

4.1.2 with metabolic activation

[redacted]

4.2 Cytotoxicity

[redacted]

Section A6.6.1/6.6.2/ 6.6.3

Annex Pt IIA VI.6.6.1/02

Genotoxicity in vitro

Bacterial reverse mutation test

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

[redacted]

5.2 Results and discussion

The increases observed in strains TA1535, TA1537, TA1538 or TA98 in the first three assays were never independently confirmed and are considered to be statistical aberrations or artifactual in nature. Therefore, the results for PH3 were negative in the Ames/Salmonella Plate Incorporation Assay under the conditions, and according to the criteria, of the test protocol

5.3 Conclusion

5.3.1 Reliability [redacted]

5.3.2 Deficiencies [redacted]

Section A6.6.1/6.6.2/ 6.6.3

Genotoxicity in vitro

Bacterial reverse mutation test

Annex Pt IIA VI.6.6.1/02

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	[redacted]
Materials and Methods	[redacted]
Results and discussion	
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.6.1/6.6.2/ 6.6.3 Genotoxicity in vitro

Bacterial reverse mutation test

Annex Pt IIA VI.6.6.1/02

Table A6_6_1-1.Table for Gene Mutation Assay (modify if necessary)

Concentration [µg/ml or other]	Number of mutant cells		Comments *give information on cytotoxicity or other*
	— S9	+ S9	
0			
x			
xx			

Table A6_6_1-2.Table for Cytogenetic In-Vitro-Test: Chromosomal Analysis (modify if necessary)

		control	low dose	mid dose	high dose
cytotoxicity *specify measure of cytotoxicity*		yes/no	yes/no	yes/no	yes/no
state mean and standard deviations below					
chromatid aberrations	gaps				
	breaks				
	interchanges				
Isochromatid aberrations	gaps				
	breaks				
	interchanges				
mitotic index					
polyploidy					
endo reduplication					

Section A6.6.1/6.6.2/ 6.6.3 Genotoxicity in vitro

In-vitro cytogenicity study in mammalian cells

Annex Pt IIA VI.6.6.1/03

Official use only

1 REFERENCE

1.1	**Reference**	[redacted] Structural Chromosome Abberation Chinese Hamster Ovary (CHO) Cell induced by Hydrogen Phsophide (PH_3), [redacted]
1.2	**Data protection**	[redacted]
1.2.1	Data owner	Detia Freyberg GmbH
1.2.2		
1.2.3	Criteria for data protection	[redacted]

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	[redacted]
2.2	**GLP**	[redacted]
2.3	**Deviations**	[redacted]

3 MATERIALS AND METHODS

3.1	**Test material**	[redacted]
3.1.1	Lot/Batch number	[redacted]
3.1.2	Specification	[redacted]

Section A6.6.1/6.6.2/ 6.6.3 Genotoxicity in vitro

In-vitro cytogenicity study in mammalian cells

Annex Pt IIA VI.6.6.1/03

3.1.2.1	Description	[redacted]
3.1.2.2	Purity	[redacted]
3.1.2.3	Stability	[redacted]
3.2	**Study Type**	[redacted]
3.2.1	Organism/cell type	[redacted]
3.2.2	Deficiencies / Proficiencies	[redacted]
3.2.3	Metabolic activation system	[redacted]
3.2.4	Positive control	[redacted]
3.3	**Administration / Exposure; Application of test substance**	
3.3.1	Concentrations	[redacted]
3.3.2	Way of application	[redacted]
3.3.3	Pre-incubation time	[redacted]
3.3.4	Other modifications	[redacted]
3.4	**Examinations**	[redacted]
3.4.1	Number of cells evaluated	[redacted]

Section A6.6.1/6.6.2/ 6.6.3 **Genotoxicity in vitro**

In-vitro cytogenicity study in mammalian cells

Annex Pt IIA VI.6.6.1/03

4 RESULTS AND DISCUSSION

4.1 Genotoxicity

4.1.1 without metabolic activation [redacted]

4.1.2 with metabolic activation [redacted]

4.2 Cytotoxicity [redacted]

[redacted]

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods [redacted]

5.2 Results and discussion

In conclusion, PH_3 did not produce any statistical significance at the 18 and 26-hour time intervals with and without S-9 mix. However, PH_3 induced statistically significant increase in aberrations per cell at 2500 (2733) and 5000 (4957) ppm without S-9 mix at the 8 hour time interval. Since BD produced a weak statistical increase at 8-hour time interval and none at the 18-hour time interval, it appears the S-9 mix is either detoxifying the BD or it was not tested at the appropriate dose to induce structural chromosomal aberrations. Also, it is possible that PH_3 at the highest dose tested, inactivated the S-9 mix.

5.3 Conclusion

5.3.1 Reliability [redacted]

5.3.2 Deficiencies [redacted]

Evaluation by Competent Authorities

EVALUATION BY RAPPORTEUR MEMBER STATE

Date [redacted]

Materials and Methods [redacted]

Section A6.6.1/6.6.2/ 6.6.3 Genotoxicity in vitro

In-vitro cytogenicity study in mammalian cells

Annex Pt IIA VI.6.6.1/03

Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	

	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A6_6_1-1.Table for Gene Mutation Assay (modify if necessary)

Concentration [µg/ml or other]	Number of mutant cells		Comments *give information on cytotoxicity or other*
	— S9	+ S9	
0			
x			
xx			

Table A6_6_1-2.Table for Cytogenetic In-Vitro-Test: Chromosomal Analysis (modify if necessary)

	control	low dose	mid dose	high dose
cytotoxicity *specify measure of cytotoxicity*	yes/no	yes/no	yes/no	yes/no

Section A6.6.1/6.6.2/ 6.6.3 Genotoxicity in vitro

In-vitro cytogenicity study in mammalian cells

Annex Pt IIA VI.6.6.1/03

state mean and standard deviations below					
chromatid aberrations	gaps				
	breaks				
	interchanges				
Isochromatid aberrations	gaps				
	breaks				
	interchanges				
mitotic index					
polyploidy					
endo reduplication					

Section A6.6.1/6.6.2/ 6.6.3 Genotoxicity in vitro

In-vitro gene mutation assay in mammalian cells

Annex Pt IIA VI.6.6.1/04

Official use only

1 REFERENCE

1.1	**Reference**	[redacted] PHOSPHINE. MUTAGENICITY STUDY IN MAMMALIAN CELLS (V79) IN VITRO – HGPRT-Test, [redacted]
1.2	**Data protection**	[redacted]
1.2.1	Data owner	Detia Freyberg GmbH
1.2.2		
1.2.3	Criteria for data protection	[redacted]

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	[redacted]
2.2	**GLP**	[redacted]
2.3	**Deviations**	[redacted]

3 MATERIALS AND METHODS

3.1	**Test material**	[redacted]
3.1.1	Lot/Batch number	[redacted]
3.1.2	Specification	[redacted]
3.1.2.1	Description	[redacted]
3.1.2.2	Purity	[redacted]
3.1.2.3	Stability	[redacted]
3.2	**Study Type**	[redacted]
3.2.1	Organism/cell type	[redacted]
3.2.2	Deficiencies / Proficiencies	[redacted]
3.2.3	Metabolic activation system	[redacted]
3.2.4	Positive control	[redacted]

Section A6.6.1/6.6.2/ 6.6.3 Genotoxicity in vitro

In-vitro gene mutation assay in mammalian cells

Annex Pt IIA VI.6.6.1/04

3.3	**Administration / Exposure; Application of test substance**	
3.3.1	Concentrations	[redacted]
3.3.2	Way of application	[redacted]
3.3.3	Pre-incubation time	[redacted]
3.3.4	Other modifications	[redacted]
3.4	**Examinations**	[redacted]
3.4.1	Number of cells evaluated	[redacted]

4 RESULTS AND DISCUSSION

4.1	**Genotoxicity**	
4.1.1	without metabolic activation	[redacted]
4.1.2	with metabolic activation	[redacted]
4.2	**Cytotoxicity**	[redacted]

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	[redacted]
5.2	**Results and discussion**	Under the present test conditions Phosphine tested up to an exposure concentration of 6580 ppm in the air in the absence and presence of metabolic activation in two independent experiments was negative in the V79 mammalian HGPRT cell mutagenicity test under conditions where the positive controls exerted potent mutagenic effects.
5.3	**Conclusion**	
5.3.1	Reliability	[redacted]
5.3.2	Deficiencies	[redacted]

Section A6.6.1/6.6.2/ 6.6.3 Genotoxicity in vitro

In-vitro gene mutation assay in mammalian cells

Annex Pt IIA VI.6.6.1/04

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	[redacted]
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A6_6_1-1.Table for Gene Mutation Assay (modify if necessary)

Section A6.6.1/6.6.2/ 6.6.3 Genotoxicity in vitro

In-vitro gene mutation assay in mammalian cells

Annex Pt IIA VI.6.6.1/04

Concentration [µg/ml or other]	Number of mutant cells		Comments *give information on cytotoxicity or other*
	— S9	+ S9	
0			
x			
xx			

Table A6_6_1-2.Table for Cytogenetic In-Vitro-Test: Chromosomal Analysis (modify if necessary)

		control	low dose	mid dose	high dose
cytotoxicity *specify measure of cytotoxicity*		yes/no	yes/no	yes/no	yes/no
state mean and standard deviations below					
chromatid aberrations	gaps				
	breaks				
	interchanges				
Isochromatid aberrations	gaps				
	breaks				
	interchanges				
mitotic index					
polyploidy					
endo reduplication					

Section A6.6.4/6.6.5/ 6.6.6

Genotoxicity in vivo

Cytogenetic in-vivo-test

Annex Point IIA6.6.4 / 01

Official use only

		1 REFERENCE
1.1	**Reference**	Kligerman, A.D.; et al. (1994): Cytogenetic effects of phosphine inhalation by rodents. I: Acute 6-hour exposure of mice; Environ. Mol. Mutagen. 23, 186 - 189
1.2	**Data protection**	No
1.2.1	Data owner	published
1.2.2		
1.2.3	Criteria for data protection	No data protection claimed
		2 GUIDELINES AND QUALITY ASSURANCE
2.1	**Guideline study**	Yes. Approved by the "Animal Care Committee of the Health Effects Research Laboratory of the U.S. EPA " and set by "The National Institute of Health".
2.2	**GLP**	not stated (It is not stated in this publication, if the original study was conducted according GLP, but since the investigations were carried out in 1994, it can be presumed that the study was conducted in compliance with the GLP regulations.)
2.3	**Deviations**	not applicated
		3 MATERIALS AND METHODS
3.1	**Test material**	Phosphine
3.1.1	Lot/Batch number	not stated
3.1.2	Specification	Deviating from specification given in section 2 as follows
3.1.2.1	Description	gaseous
3.1.2.2	Purity	750 ppm Phosphine in nitrogen, purity: 99.99 %
3.1.2.3	Stability	not indicated
3.1.2.4	Maximum tolerable dose	not indicated
3.2	**Test Animals**	
3.2.1	Species	mouse
3.2.2	Strain	CD-1
3.2.3	Source	Charles River Breeding Laboratories, Raleigh, NC, USA
3.2.4	Sex	male
3.2.5	Age/weight at study initiation	12 weeks approximately
3.2.6	Number of animals	5m per dose

Section A6.6.4/6.6.5/ 6.6.6 **Genotoxicity in vivo**
Cytogenetic in-vivo-test

Annex Point IIA6.6.4 / 01

	per group	
3.2.7	Control animals	Yes
3.3	**Administration/ Exposure**	inhalation
3.3.1	Number of applications	1
3.3.2	Interval between applications	6 h
3.3.3	Postexposure period	20 h after treatment
		Inhalation
3.3.4	Type	Whole-body inhalation
3.3.5	Concentration	0, 5, 10 and 15 ppm PH_3 (norminal)
		0, 5.24 ± 0.69, 9.94 ± 0.69 and 16.00 ± 1.15 (actual)
3.3.6	Vehicle	Nitrogen
3.3.7	Concentration in vehicle	750 ppm PH_3 in Nitrogen
3.3.8	Total volume applied	n. a.
3.3.9	Controls	Vehicle
3.4	**Examinations**	
3.4.1	Clinical signs	Yes
3.4.2	Tissue	bone marrow
		Number of animals: all animals
		Number of cells: not indicated
		Time points: 20 h after treatment
		Type of cells bone marrow smears
		Parameters: chromosomal aberrations (CA)
		sister chromatid exchanges (SCE)
		micronuleus (MN) formation
3.5	**Further remarks**	

4 RESULTS AND DISCUSSION

4.1	**Clinical signs**	After exposure to 15 ppm, the animals appeared lethargic and their breathing was shallow, but all survived. The controls and other exposed animals showed no outward signs of toxicity.

Section A6.6.4/6.6.5/ 6.6.6

Genotoxicity in vivo

Cytogenetic in-vivo-test

Annex Point IIA6.6.4 / 01

4.2	**Haematology / Tissue examination**	See table A6_6_4-1
4.3	**Genotoxicity**	No
4.4	**Other**	no other significant effects

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	In-vivo mutagenicity study as described in 3.
5.2	**Results and discussion**	After exposure to 15 ppm, the animals appeared lethargic and their breathing was shallow, but all survived. The controls and other exposed animals showed no outward signs of toxicity. All measures of cytogenetic damage analyzed were negative. No evidence was found of SCE, CA, or MN induction. There was also no indication of rare highly damaged cells in any of the treated animals, with the vast majority of aberrations being simple chromatid deletions. The only statistically significant effect observed was a concentration-related slowing of the cell cycle (P =0.009) in the cultured splenocytes at all exposure levels. Thus in this study, there is no evidence that PH_3 is clastogenic, aneuploidogenic, or capable of inducing SCEs at or near toxic concentrations in male mice exposed by inhalation.
5.3	**Conclusion**	
5.3.1	Reliability	1
5.3.2	Deficiencies	No

Section A6.6.4/6.6.5/ 6.6.6

Genotoxicity in vivo

Cytogenetic in-vivo-test

Annex Point IIA6.6.4 / 01

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	[redacted]
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.6.4/6.6.5/ 6.6.6 Genotoxicity in vivo

Cytogenetic in-vivo-test

Annex Point IIA6.6.4 / 01

Table A6_6_4-1. Results Table

Cytogenetic Effects of a 6-hr PH_3 Inhalation Exposure on Male CD-1 Mice							
PH_3 (ppm)	Animals	% Abnormal (CA)	SCE/ metaphase	Cell cycle (RI)	MN-PCEs/ 1000	MN_{bn}/1000	% PCEs
0	1	2	13.6	1.88	2.0	5.5	43
	2	3	10.4	1.81	2.0	5.0	53
	3	4	10.4	2.04	0.0	2.0	53
	4	3	12.0	1.71	6.0	4.0	75
	5	2	10.4	1.89	2.0	7.5	43
	0 ± s.d.	2.8 ± 0.8	11.4 ± 1.4	1.87 ± 0.12	2.6 ± 2.2	4.8 ± 2.0	53± 13
5	1	2	9.1	1.67	4.0	5.7	70
	2	2	10.5	1.69	5.0	5.5	73
	3	4	8.4	1.76	1.0	3.5	62
	4	3	12.2	1.72	6.0	4.5	47
	5	1	10.2	1.53	4.0	8.0	40
	0 ± s.d.	2.4 ± 1.1	10.1 ± 1.5	1.67 ± 0.09*	4.0 ± 1.9	5.4 ± 1.7	58 ± 14
	1	1	7.7	1.38	2.0	5.5	65
	2	1	11.6	1.57	2.0	2.5	40
	3	1	11.9	1.87	2.0	5.0	54
	4	0	10.2	1.66	3.0	5.5	49
	5	0	10.5	1.56	2.0	5.5	45
	0 ± s.d.	0.6 ± 0.5	10.4 ± 1.6	1.61 ± 0.18*	2.2 ± 0.4	4.8 ± 1.3	50 ± 9
15	1	2	12.3	1.54	1.0	4.5	50
	2	0	11.4	1.62	3.0	6.5	40
	3	0	10.0	1.49	3.0	8.5	34
	4	2	11.3	1.71	2.0	3.0	67
	5	1	12.2	1.46	0.0	6.0	33
	0 ± s.d.	1.0 ± 1.0	11.4 ± 0.9	1.56 ± 0.10*	1.8 ± 1.3	5.7 ± 2.1	45 ± 14

* statistically significant ($p < 0.05$)

Section A6.6.4/6.6.5/ 6.6.6

Genotoxicity in vivo

Cytogenetic in-vivo test

Annex Point IIA6.6.4 / 02

Official use only

1 REFERENCE

1.1	**Reference**	Kligerman, A.D.; et al. (1994): Cytogenetic and germ cell effects of phosphine inhalation by rodents: II. Sub-acute exposure to rats and mice; Environ. Mol. Mutagen. 24, 301 - 306
1.2	**Data protection**	No
1.2.1	Data owner	published
1.2.2		
1.2.3	Criteria for data protection	No data protection claimed

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	Yes. Approved by the "Animal Care Committee of the Health Effects Research Laboratory of the U.S. EPA " and set by "The National Institute of Health".
2.2	**GLP**	not stated (It is not stated in this publication, if the original study was conducted according GLP, but since the investigations were carried out in 1994, it can be presumed that the study was conducted in compliance with the GLP regulations.)
2.3	**Deviations**	No

3 MATERIALS AND METHODS

3.1	**Test material**	Phosphine
3.1.1	Lot/Batch number	not stated
3.1.2	Specification	Deviating from specification given in section 2 as follows
3.1.2.1	Description	gaseous
3.1.2.2	Purity	21500 ppm Phosphine in nitrogen.
3.1.2.3	Stability	not indicated
3.1.2.4	Maximum tolerable dose	not indicated
3.2	**Test Animals**	
3.2.1	Species	mouse and rat
3.2.2	Strain	B6C3F1 mice and F344/N rats
3.2.3	Source	Mice: Charles River Breeding Laboratories, Raleigh , NC, USA Rat: Charles River Breeding Laboratories, Portage, MI, USA
3.2.4	Sex	male

Section A6.6.4/6.6.5/ 6.6.6 Genotoxicity in vivo

Cytogenetic in-vivo test

Annex Point IIA6.6.4 / 02

3.2.5	Age/weight at study initiation	Approximately 8 weeks
3.2.6	Number of animals per group	5m per dose
3.2.7	Control animals	Yes
3.3	**Administration/ Exposure**	Inhalation
3.3.1	Number of applications	6 hr/day for 9 days over an 11-day period
3.3.2	Interval between applications	5 days exposed, 2 days off, 4 days exposed
3.3.3	Postexposure period	18 to 20 h after treatment
		Inhalation
3.3.4	Type	whole-body inhalation
3.3.5	Concentration	0, 1.25, 2.5 and 5 ppm PH_3
3.3.6	Vehicle	Nitrogen
3.3.7	Concentration in vehicle	21,500 ppm PH_3 in nitrogen
3.3.8	Total volume applied	not indicated
3.3.9	Controls	Vehicle
3.4	**Examinations**	
3.4.1	Clinical signs	not indicated
3.4.2	Tissue	bone marrow, peripheral blood
		Number of animals: all
		Number of cells: not indicated
		Time points: 18 to 20 h after treatment
		Type of cells bone marrow smears (rat)
		peripheral blood (rat and mice)
		In mice, isolated mononuclear leucocytes were analysed for sister chromatid exchange (SCE); chromosomal aberrations (CA) were determined in peripheral blood cells (PBL), and micronucleus (MN) formation in binucleated (BN) lymphocytes and polychromatic erythrocytes (PCE). Bone marrow smears of rats were analysed for micronucleated PCEs, and peripheral blood was investigated for SCE and CA.
3.5	**Further remarks**	

Section A6.6.4/6.6.5/ 6.6.6 **Genotoxicity in vivo**

Cytogenetic in-vivo test

Annex Point IIA6.6.4 / 02

4 RESULTS AND DISCUSSION

4.1	**Clinical signs**	not indicated
4.2	**Haematology / Tissue examination**	See tables A6_6_4-1 and A6_6_4-2
4.3	**Genotoxicity**	No
4.4	**Other**	no other significant effect

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	In vivo cytogenetic study as described in 3
5.2	**Results and discussion**	Mouse (table A6_6_4-1): PH3 inhalation caused no statistically significant increases in SCE or CAs in PBLs. Or MN in peripheral blood PCEs or BN lymphocytes. In addition, all of the CAs observed were either simple chromatid or chromosome deletions and no highly damaged cells or complex exchanges were seen. As an additional verification of the MN data the mouse peripheral blood normochromatic erythrocytes (NCEs) were scored for MN induction. No statistically significant increases were found (data not shown). Rat (table A6_6_4-2): Cytogenetic results for the rat were similar to those observed with the mouse. There were no statistically significant increases in SCEs or CAs in PBLs or MN data, the rat bone marrow NCEs were scored for MN induction. No statistically increases were found (data not shown). Therefore, there is no evidence that PH3 causes cytogenetic damage in mice or rats under the conditions of this test.
5.3	**Conclusion**	
5.3.1	Reliability	1
5.3.2	Deficiencies	No

Section A6.6.4/6.6.5/ 6.6.6 Genotoxicity in vivo

Cytogenetic in-vivo test

Annex Point IIA6.6.4 / 02

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	[redacted]
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A6_6_4-1. Cytogenetic Effects of Phosphine inhalation in the Peripheral Blood of Mice

Phosphine (ppm)	SCEs/ metaphase (PBL)	Aberrant metaphases (PBL) (%)	MN/ 1000 PCEs	MN-BN PBL/1000	Replicative index (PBL)	PCEs (%)
0	8.9 ± 0.5 (5)	1.2 ± 1.1 (5)	4.1 ± 1.7 (5)	2.3 ± 1.3 (5)	1.48 ± 0.12 (5)	8 ± 2 (5)
1.25	8.9 ± 0.5 (4)	2.5 ± 2.6 (4)	4.4 ± 1.1 (5)	2.6 ± 1.7 (5)	1.47 ± 0.24 (4)	8 ± 2 (5)
2.5	9.2 ± 0.7 (3)	2.0 ± 1.2 (5)	4.4 ± 1.5 (5)	4.5 ± 2.2 (5)	1.48 ± 0.27 (3)	7 ± 2 (5)
5.0	9.1 ± 0.6 (4)	1.2 ± 1.6 (5)	2.6 ± 0.2 (5)	2.2 ± 1.0 (5)	1.52 ± 0.06 (4)	6 ± 3 (5)

Table A6_6_4-2. Cytogenetic Effects of Phosphine inhalation in the Peripheral Blood and Bone Marrow of Rats

Phosphine (ppm)	SCEs/ metaphase (PBL)	Aberrant metaphases (PBL) (%)	MN/ 1000 bone marrows PCEs	Replicative index (PBL)	PCEs (%)
0	7.9 ± 0.3 (5)	1.8 ± 1.5 (5)	1.5 ± 0.6 (5)	1.53 ± 0.10 (5)	57 ± 5 (5)
1.25	8.4 ± 0.6 (5)	2.2 ± 2.3 (5)	0.6 ± 0.5 (5)	1.48 ± 0.10 (5)	62 ± 7 (5)
2.5	8.4 ± 0.6 (4)	2.5 ± 0.6 (4)	1.4 ± 0.9 (5)	1.64 ± 0.08 (4)	66 ± 6 (5)
5.0	8.2 ± 0.2 (5)	1.6 ± 1.1 (5)	2.0 ± 1.0 (5)	1.39 ± 0.17 (5)	59 ± 10 (5)

Section A 6.6.5 Genotoxicity in vivo

Annex Point IIA VI.6.6.5

Unscheduled DNA Synthesis in primary hepatocytes in-vivo / in-vitro

Official use only

1 REFERENCE

1.1	**Reference**	[redacted] GENOTOXICITY TEST ON PHOSPHINE IN THE IN VIVO /IN VITRO ASSAY FOR UNSCHEDULED DNA SYNTHESIS IN RAT PRIMARY HEPATOCYTE CULTURES AT TWO TIMEPOINTS, [redacted]
1.2	**Data protection**	[redacted]
1.2.1	Data owner	Detia Freyberg GmbH
1.2.2		
1.2.3	Criteria for data protection	[redacted]

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	[redacted]
2.2	**GLP**	[redacted]
2.3	**Deviations**	[redacted]

3 MATERIALS AND METHODS

3.1	**Test material**	[redacted]
3.1.1	Lot/Batch number	[redacted]
3.1.2	Specification	[redacted]
3.1.2.1	Description	[redacted]
3.1.2.2	Purity	[redacted]
3.1.2.3	Stability	[redacted]
3.1.2.4	Maximum tolerable dose	[redacted]

3.2	**Test Animals**	
3.2.1	Species	[redacted]
3.2.2	Strain	[redacted]
3.2.3	Source	[redacted]
3.2.4	Sex	[redacted]
3.2.5	Age/weight at study initiation	[redacted]
3.2.6	Number of animals per group	[redacted]
3.2.7	Control animals	[redacted]
3.3	**Administration/ Exposure**	[redacted]
3.3.1	Number of applications	[redacted]
3.3.2	Interval between applications	[redacted]
3.3.3	Postexposure period	[redacted]
3.3.4	Type	[redacted]
3.3.5	Concentration	[redacted]
3.3.6	Vehicle	[redacted]
3.3.7	Concentration in vehicle	[redacted]
3.3.8	Total volume applied	[redacted]
3.3.9	Controls	[redacted]
3.4	**Examinations**	
3.4.1	Clinical signs	[redacted]
3.4.2	Tissue	[redacted]
3.5	**Further remarks**	

4 RESULTS AND DISCUSSION

4.1	**Clinical signs**	Labored breathing was seen in the animals exposed to 18 and 23 ppm of phosphine. A 5 to 7 percent weight loss was seen in the animals exposed to 13, 18 and 23 ppm.
4.2	**Haematology / Tissue examination**	n. a.
4.3	**Genotoxicity**	No
4.4	**Other**	see 4.1

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	[redacted]
5.2	**Results and discussion**	[redacted]
5.3	**Conclusion**	
5.3.1	Reliability	[redacted]
5.3.2	Deficiencies	[redacted]

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	[redacted]
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A6_6_4-1. Table for Micronucleus Test In Vivo (modify if necessary)

State mean ± standard deviation state individual numbers for critical findings		control group	low dose			mid dose			high dose		
Number of cells evaluated											
Sampling time (h)											
Number of erythrocytes	normochromatic										
	polychromatic										
	polychromatic with micronuclei										
Ratio of erythrocytes	polychromatic / normochromatic										
	polychromatic with micronuclei / normochromatic										

Table A6_6_4-2. **Table for Cytogenetic In-Vivo-Test: Chromosomal Analysis (modify if necessary) in: erythrocytes / lymphocytes spermatogonia / other**

State mean ± standard deviation *state individual numbers for critical findings*		control group	low dose			mid dose			high dose		
Sampling time (h)			12	18	24	12	18	24	12	18	24
Number of cells evaluated											
Toxicity, specify effects											
Chromatid aberrations	**gaps**										
	breaks										
	interchanges										
Isochromatid aberrations	**gaps**										
	breaks										
	interchanges										
Mitotic index											
Polyploidy											
Endo reduplication											

Section A6.7 Carcinogenicity

Annex Point IIA6.7

Official use only

1 REFERENCE

1.1 Reference

[redacted] 2-YEAR COMBINED INHALATION CHRONIC TOXICITY AND ONCOGENICITY STUDY OF PHOSPHINE IN RATS, [redacted]

1.2 Data protection

[redacted]

1.2.1 Data owner: Detia Freyberg GmbH

1.2.2 Companies with letter of access: [redacted]

1.2.3 Criteria for data protection: [redacted]

2 GUIDELINES AND QUALITY ASSURANCE

2.1 Guideline study

[redacted]

2.2 GLP

[redacted]

2.3 Deviations

[redacted]

Evaluation by Competent Authorities

EVALUATION BY RAPPORTEUR MEMBER STATE

Date [redacted]

Materials and Methods [redacted]

Results and discussion [redacted]

Conclusion No evidence for a carcinogenic potential, [redacted]

Reliability [redacted]

Acceptability [redacted]

Remarks

Section A6.7 Carcinogenicity

Annex Point IIA6.7

	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.5/6.7 Annex Point IIA VI 6.5/6.7	Chronic toxicity/Carcinogenicity study, other mammalian	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA *As outlined in the TNsG on data requirements, the applicant must always be able to justify the suggested exemptions from the data requirements. The justifications are to be included in the respective location (section) of the dossier.* *If one of the following reasons is marked, detailed justification has to be given below. General arguments are not acceptable*	Official use only
Other existing data [X]	**Technically not feasible [ ]** **Scientifically unjustified [X]**	
Limited exposure [X]	**Other justification [ ]**	

Detailed justification:

[redacted]

Section A6.5/6.7 Chronic toxicity/Carcinogenicity study, other mammalian
Annex Point IIA VI 6.5/6.7

[redacted]

Undertaking of intended data submission [ ]

Evaluation by Competent Authorities

EVALUATION BY RAPPORTEUR MEMBER STATE

Date [redacted]

Evaluation of applicant's justification [redacted]

Section A6.5/6.7 Annex Point IIA VI 6.5/6.7	Chronic toxicity/Carcinogenicity study, other mammalian
	[redacted]
Conclusion	[redacted]
Remarks	
	COMMENTS FROM OTHER MEMBER STATE *(specify)*
Date	*Give date of comments submitted*
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.8.1 Teratogenicity Study

Annex Point IIA VI.6.8.1 *(Inhalation)*

Official use only

1 REFERENCE

1.1 Reference [redacted] An Inhalation Developmental Toxicity Study of Phosphine (PH_3) in Rats, [redacted]

1.2 Data protection [redacted]

1.2.1 Data owner: Detia Freyberg GmbH

1.2.2 Companies with letter of access: [redacted]

1.2.3 Criteria for data protection: [redacted]

2 GUIDELINES AND QUALITY ASSURANCE

2.1 Guideline study [redacted]

2.2 GLP [redacted]

2.3 Deviations [redacted]

3 MATERIALS AND METHODS

3.1 Test material [redacted]

3.1.1 Lot/Batch number: [redacted]

3.1.2 Specification: [redacted]

3.1.2.1 Description: [redacted]

3.1.2.2 Purity: [redacted]

3.1.2.3 Stability: [redacted]

3.2 Test Animals

3.2.1 Species: [redacted]

3.2.2 Strain: [redacted]

3.2.3 Source: [redacted]

3.2.4 Sex: [redacted]

3.2.5 Age/weight at study initiation: [redacted]

3.2.6 Number of animals per group: [redacted]

Section A6.8.1 Teratogenicity Study

(Inhalation)

Annex Point IIA VI.6.8.1

3.2.7	Control animals	[redacted]
3.2.8	Mating period	[redacted]
3.3	**Administration/ Exposure**	[redacted]
3.3.1	Duration of exposure	[redacted]
3.3.2	Postexposure period	[redacted]
		Inhalation
3.3.3	Concentrations	[redacted]
3.3.4	Particle size	[redacted]
3.3.5	Type or preparation of particles	[redacted]
3.3.6	Type of exposure	[redacted]
3.3.7	Vehicle	[redacted]
3.3.8	Concentration in vehicle	[redacted]
3.3.9	Exposure period / day	[redacted]
3.3.10	Controls	[redacted]
3.4	**Examinations**	
3.4.1	Body weight	[redacted]
3.4.2	Food consumption	[redacted]
3.4.3	Clinical signs	[redacted]
3.4.4	Examination of uterine content	[redacted]
3.4.5	Examination of foetuses	
3.4.5.1	General	[redacted]
3.4.5.2	Skelet	[redacted]
3.4.5.3	Soft tissue	[redacted]
3.5	**Further remarks**	

Section A6.8.1 **Teratogenicity Study**
(Inhalation)
Annex Point IIA VI.6.8.1

4 RESULTS AND DISCUSSION

4.1	**Maternal toxic Effects**	[redacted]
4.2	**Teratogenic / embryotoxic effects**	[redacted]
4.3	**Other effects**	[redacted]

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	[redacted]
5.2	**Results and discussion**	No maternally toxic, embryotoxic, fetotoxic or teratogenic effects were observed.
5.3	**Conclusion**	
5.3.1	LO(A)EL maternal toxic effects	[redacted]
5.3.2	NO(A)EL maternal toxic effects	[redacted]
5.3.3	LO(A)EL embryotoxic / teratogenic effects	[redacted]
5.3.4	NO(A)EL embryotoxic / teratogenic effects	[redacted]
5.3.5	Reliability	[redacted]
5.3.6	Deficiencies	[redacted]

Section A6.8.1 Teratogenicity Study

(Inhalation)

Annex Point IIA VI.6.8.1

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	[redacted]
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Reliability	[redacted]
Acceptability	[redacted]
Remarks	
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.8.1 Annex Point IIA VI 6.8.1	Teratogenic test, rabbit	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA *As outlined in the TNsG on data requirements, the applicant must always be able to justify the suggested exemptions from the data requirements. The justifications are to be included in the respective location (section) of the dossier.* *If one of the following reasons is marked, detailed justification has to be given below. General arguments are not acceptable*	Official use only
Other existing data [X]	**Technically not feasible [ ]** **Scientifically unjustified [X]**	
Limited exposure [X]	**Other justification [ ]**	
Detailed justification:		

[redacted]

Section A6.8.1 Teratogenic test, rabbit

Annex Point IIA VI 6.8.1

[redacted]

Section A6.8.1 Teratogenic test, rabbit

Annex Point IIA VI 6.8.1

[redacted]

Undertaking of intended data submission [ ]	*Give date on which the data will be handed in later (Only acceptable if test or study is already being conducted and the responsible CA has agreed on the delayed data submission.)*
	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	[redacted]
Evaluation of applicant's justification	[redacted]
Conclusion	[redacted]
Remarks	
	COMMENTS FROM OTHER MEMBER STATE *(specify)*
Date	*Give date of comments submitted*
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.8.2 Annex Point IIA6.8.2	Two generations reproduction study	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ]	Technically not feasible [ ]	Scientifically unjustified [ ]
Limited exposure [X]	Other justification [X]	

Detailed justification:

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	[redacted]
Evaluation of applicant's justification	[redacted]
Conclusion	[redacted]
Remarks	
	COMMENTS FROM OTHER MEMBER STATE *(specify)*
Date	*Give date of comments submitted*
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

G:\Abteilung-6\0 Substanzen\P\Phosphorwasserstoff und Phosphide\Calciumphosphid\Aluminiumphosphid\8 Biozide EU-Bewertung\PA 18-Erg.D\Firma Detia\1 CA-Report\2 BWP 2\Versand\Doc III\active substance\06_Toxicology\A6_08_2_non-sub_AlP_002.rtf

Section A6.9 Delayed Neurotoxicity

Annex Point IIIA VI.1

Official use only

1 REFERENCE

1.1	**Reference**	[redacted] ACUTE NEUROTOXICITY STUDY IN RATS, [redacted]
1.2	**Data protection**	[redacted]
1.2.1	Data owner	Detia Freyberg GmbH
1.2.2	Companies with letter of access	[redacted]
1.2.3	Criteria for data protection	[redacted]

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	[redacted]
2.2	**GLP**	[redacted]
2.3	**Deviations**	[redacted]

3 MATERIALS AND METHODS

3.1	**Test material**	[redacted]
3.1.1	Lot/Batch number	[redacted]
3.1.2	Specification	[redacted]
3.1.2.1	Description	[redacted]
3.1.2.2	Purity	[redacted]
3.1.2.3	Stability	[redacted]
3.2	**Reference Substance (positive control)**	[redacted]

Section A6.9 Delayed Neurotoxicity

Annex Point IIIA VI.1

3.3	**Test Animals**	
3.3.1	Species	[redacted]
3.3.2	Strain	[redacted]
3.3.3	Source	[redacted]
3.3.4	Sex	[redacted]
3.3.5	Rearing conditions	[redacted]
3.3.6	Age/weight at study initiation	[redacted]
3.3.7	Number of animals per group	[redacted]
3.3.8	Control animals	[redacted]
3.4	**Administration**	[redacted]
3.4.1	Exposure	[redacted]
3.4.2	Dose Levels	[redacted]
3.4.3	Vehicle	[redacted]
3.4.4	Concentration in vehicle	[redacted]
3.4.5	Total volume applied	[redacted]
3.4.6	Postexposure period	[redacted]
3.4.7	Anticholinergic substances used	[redacted]
3.4.8	Controls	[redacted]
3.5	**Examinations**	
3.5.1	Body Weight	[redacted]
3.5.2	Signs of Toxicity	[redacted] response, air righting reflex, thermal response, hind foot splay [redacted]

Section A6.9 Delayed Neurotoxicity

Annex Point IIIA VI.1

3.5.3 Observation schedule

[redacted]

3.5.4 Clinical Chemistry

[redacted]

3.5.5 Pathology

[redacted]

3.5.6 Histopathology

[redacted]

3.6 Further remarks

Section A6.9 Delayed Neurotoxicity

Annex Point IIIA VI.1

4 RESULTS AND DISCUSSION

4.1 Body Weight

[redacted]

4.2 Clinical signs of toxicity

[redacted]

4.3 Clinical Chemistry

[redacted]

4.4 Pathology

[redacted]

4.5 Histopathology

[redacted]

4.6 Other

[redacted]

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

[redacted]

Section A6.9 Delayed Neurotoxicity

Annex Point IIIA VI.1

5.2 Results and discussion

[redacted]

5.3 Conclusion

5.3.1 LOAEL [redacted]

5.3.2 NOAEL [redacted]

5.3.3 Reliability [redacted]

5.3.4 Deficiencies [redacted]

Evaluation by Competent Authorities

EVALUATION BY RAPPORTEUR MEMBER STATE

Date [redacted]

Materials and Methods [redacted]

Results and discussion NOAEL = 38 ppm with regard to anatomic pathology and the behavioral and neurological status observed in the functional observational battery, [redacted] NOAEL < 21 ppm (with regard to changes in motor activity on day 1)

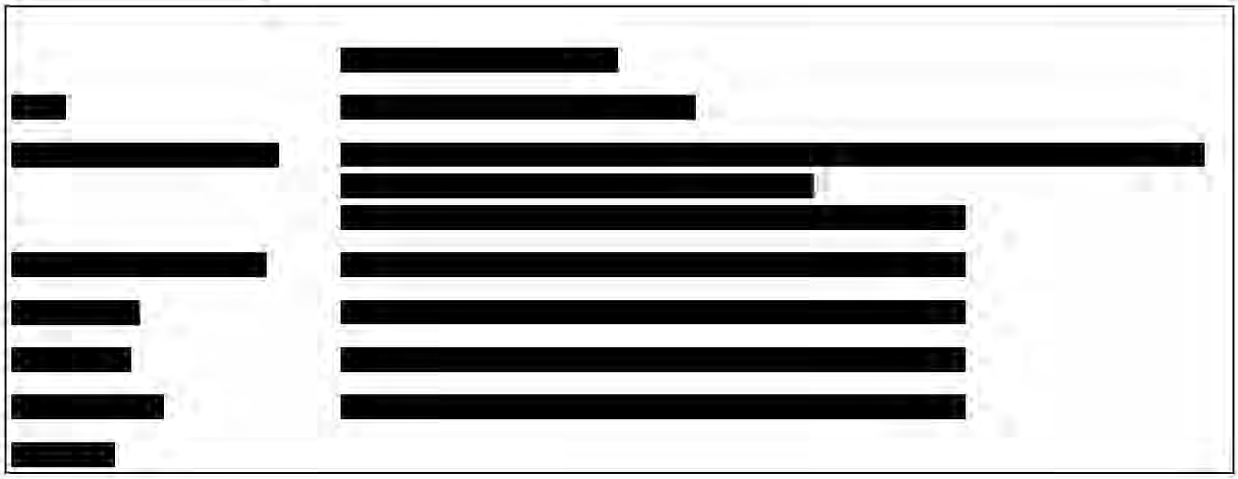
Conclusion [redacted]

Reliability [redacted]

Acceptability [redacted]

Remarks

[redacted]



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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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		[redacted]	[redacted]	[redacted]	[redacted]

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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Section A6.9/02 Subchronic Neurotoxicity in Rats

Annex Point IIIA VI.1

Official use only

1 REFERENCE

1.1	**Reference**	Schaefer,G.J. et al. (1998), Acute and Subchronic Inhalation Neurotoxicity of Phosphine in the Rat, Inhalation Toxicology 10 (4), 293-320. Published **Please note: This summary only refers to the subchronic section of the above publication. For details regarding the acute part, cf. document IIIA-6.9.**
1.2	**Data protection**	No
1.2.1	Data owner	N/A
1.2.2	Companies with letter of access	N/A
1.2.3	Criteria for data protection	N/A

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	No, but comparable to OECD 424
2.2	**GLP**	Yes (not stated in this publication, but provided with the original study report of the acute section which was submitted by the participant for this CA report – cf. Doc. IIIA 6.9)
2.3	**Deviations**	None significant

3 MATERIALS AND METHODS

3.1	**Test material**	Phosphine
3.1.1	Lot/Batch number	Not stated
3.1.2	Specification	See below
3.1.2.1	Description	Gaseous phosphine diluted with nitrogen, manufactured by: Scott Specialty Gases, South Plainfield, NJ, USA)
3.1.2.2	Purity	1 % phosphine in nitrogen (based on considerations reflecting the lower explosive limit of phosphine gas)
3.1.2.3	Stability	Not stated in this publication, but confirmed by other experiments.
3.2	**Reference Substance (positive control)**	None

Section A6.9/02 Subchronic Neurotoxicity in Rats

Annex Point IIIA VI.1

3.3	**Test Animals**	
3.3.1	Species	Rat
3.3.2	Strain	Crl: CD BRVAF/Plus
3.3.3	Source	Charles River Laboratories, Portage, MI, USA
3.3.4	Sex	Male/female
3.3.5	Rearing conditions	Open wire mesh cages with stainless steel floors
3.3.6	Age/weight at study initiation	Age: 7-8 wk Weight: 225-344/164-228 g (males/females)
3.3.7	Number of animals per group	16/16 (males/females), 6 additional animals/sex in control and high-dose groups (2-wk recovery experiment)
3.3.8	Control animals	Yes
3.4	**Administration**	
3.4.1	Exposure	Inhalation, whole-body exposure, 6 h/d, 5 d/wk, for 13 wk
3.4.2	Dose Levels	0.3/1.0/3.0 ppm PH_3
3.4.3	Vehicle	Posphine (PH_3) in nitrogen, diluted in air
3.4.4	Concentration in vehicle	1 % phosphine in nitrogen
3.4.5	Total volume applied	N/A
3.4.6	Postexposure period	14 d
3.4.7	Anticholinergic substances used	N/A
3.4.8	Controls	Air
3.5	**Examinations**	
3.5.1	Body Weight	Yes, at least once prior to initiation of test exposures and weekly thereafter. Food consumption: weekly.
3.5.2	Signs of Toxicity	All animals were observed at least twice per day for morbidity, mortality, injury, and availability of food and water. Any animal in poor health was identified for further monitoring and possible euthanasia. A detailed clinical examination of each animal was performed once during each study week. The examination included, but was not limited to observations of the general condition, skin, fur, eyes, ears, nose, oral cavity, thorax, abdomen, external genitalia, limbs, and feet, as well as evaluation of respiration and palpation of tissue masses.

Section A6.9/02 Subchronic Neurotoxicity in Rats

Annex Point IIIA VI.1

3.5.3	Neurobehavioural and Functional Observational Battery Evaluations	Behavioural tests were conducted on 11 animals/sex/group, which were randomly selected. Neurobehavioural tests were conducted on these same animals as well as on the additional 6 animals/sex/group from the 14-d recovery experiment (control and high-dose, cf. 3.3.7). FOB evaluations were conducted prior to initiation of exposure to the test article, and during wk 4, 8, and 13 of test article administration. During wk 4, 8, and 13 the animals were tested on Tuesday through Friday of the exposure week in a staggered fashion. On each of these days an approximately equal number of animals from each group was tested. In addition, recovery animals (cf. above) were evaluated approximately 2 wk after the end of the last exposure period. Each animal was observed for a minimum of 3 min. in a black Plexiglas, open-field observation box measuring 20 x 20 x 8 inches. the following evaluations were conducted: 1. Assessment of signs of autonomic function (lacrimation, salivation, piloerection, exophthalmus, measurement of urination and defecation, pupillary function), severity scores ranging from none to severe 2. Convulsions, tremors, or degree of palpebral closure, abnormal movements, both in the home cage and in the open field (description, incidence, severity) 3. Reactivity to general stimuli, such as removal from the cage or handling (scoring scale from no reaction to hyperactivity) 4. Arousal level during observations of the unperturbed subject in the open field, (coma to hyperalertness) 5. Posture and/or gait abnormalities (none to severe) 6. Fore- and hindlimb grip strength 7. Landing foot (hindfoot) splay 8. Sensorimotor responses (pain perception, heat evasion, auditory startle, sensorimotor/proprioceptive response to approaching/touching blunt object) 9. Any other unusual or abnormnla behaviour, stereotypies, emaciation, dehydration, hypo- or hypertonia, fur appearance, 10. Other observations, such as: Rearing activity in the open field, air righting, boy temperature, vocalisations, rate and ease of respiration Furthermore, motor activity was assessed in all animals subjected to the above examinations following the FOB tests. Animals were placed in a Digiscan (Omnitech Electronics, Columbus, OH, USA) activity monitor measuring 16 x 16 x 12 (height) inches and equipped with a computer analyser. Animals were recorded for 30 min. by 8 photocells each in two horizontal planes and one vertical plane. A range of different activities were recorded but only the following were used in comparisons between treated and control animals as the most representative activity parameters: horizomtal activity, vertical activity, total distance, and stereotypic time, which was operationally defined as the total time spent in repetitive movements.

Section A6.9/02 Subchronic Neurotoxicity in Rats

Annex Point IIIA VI.1

3.5.4	Clinical Chemistry	After 13 wk of exposure, blood samples from animals fasted for approx. 16 h were taken from the orbital sinus after carbon dioxide/oxygen inhalation. The following haematological parameters were evaluated: leukocyte count (total and differential), erythrocyte count, haemoglobin, haematocrit, mean corpuscular haemoglobin, mean corpuscular volume, mean corpuscular haematocrit concentration (calculated), platelet count, and reticulocyte count. The following biochemical parameters were evaluated: alkaline phosphatase, total bilirubin, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, sorbitol dehydrogenase, urea nitrogen, creatinine, total protein, albumin, globulin and albumin/globulin (A/G) ratio, glucose (fasting), total cholesterol, sodium, potassium, chloride, calcium, magnesium, phosphorus, and phosphokinase. The following urological parameters were evaluated: 16-h volume, color and appearance, pH, specific gravity, protein, glucose, ketones, urobilinogen, nitrites, bilirubin, occult blood, leukocytes, and microscopy of spun deposit.
3.5.5	Gross Pathology	6 animals/sex/group were randomly selected for neuropathology evaluations. The animals were euthanized by anaesthesia via intraperitoneal injecvtion of sodium pentobarbital to effect followed by whole-body perfusion in situ with 3 % paraformaldehyde and 3 % glutaraldehyde in 0.1 M phosphate buffer. At necropsy, both sciatic nerves with distal branches (tibial and peroneal) were dissected and affixed to labelled cards. All other tissues were eviscerated and submerged in fixative in labelled bags. Light-microscopic evaluation was performed on the following tissues: brain (cerebrum, cerebellum, pons/medulla oblongata), spinal cord at cervical and lumbar swelling, respectively, proximal sciatic nerves, peroneal nerve, tibial nerves, gasserian ganglion, cervical and lumbar dorsal root ganglia, and cervical and lumbar dorsal and ventral roots. For all other animals, a complete post-mortem examination was performed. The animals were euthanized by anaesthesia via intraperitoneal sodium pentobarbital injection to effect followed by exsanguination from the abdominal aorta. Absolute and relative organ weights were measured and calculated for the brain, adrenals, heart, kidney, liver, lung, and gonads. A full complement of organs and tissues was collected from those animals and stored for possible future examination.
3.5.6	Histopathology	Brain, spinal cord, and sciatic nerve sections collected from the neuropathology subgroups as given above were embedded in paraffin and subsequently stained. Sections of peroneal and tibial nerves were embedded in glycol methacrylate, processed to 1-µm-sections and subsequently stained.

Section A6.9/02 Subchronic Neurotoxicity in Rats

Annex Point IIIA VI.1

3.6	**Further remarks**	The following statistical analysis was conducted separately for each sex, parameter, and time period. First, Bartlett's test for homogeneity of variance was performed. In case of homogeneity, one-way ANOVA was carried out which – if significant - was followed by Dunnett's test for comparison of test and control groups. In case of non-homogeneity, a rank-transformed ANOVA was performed following by Dunn's test with a Bonferroni correction. Categorical or nominal data obtained durinfg FOB testing were analyzed using the Chi-square test for homogeneity of RxC contingency tables
		4 RESULTS AND DISCUSSION
4.1	**Body Weight**	No significant test substance-related adverse effects reported
4.2	**Clinical signs of toxicity**	Mortality In the 0.3 ppm group. 1 male died on day 101 with the cause of death unknown. In the 3 ppm group 1 male died on day 102 following blood sampling for clinical pathology and 1 female died on day 89. None of these deaths was considered phosphine-related. Clinical signs No significant test substance-related adverse effects reported
4.3	**Neurobehavioural and Functional Observational Battery Evaluations**	Behaviour/FOB No consistent or enduring test substance-related adverse effect on the behavioural or neurological status of male or female animals. Motor activity Observed differences were not attributed to phosphine exposure, as they were non-systematic, inconsistent between the sexes and were present prior to exposure to phosphine
4.4	**Clinical Chemistry, Haematology, and Urinalysis**	Haematology and Urinalysis No significant test substance-related adverse effects Clinical chemistry Mean serum chloride levels were slightly elevated as compared to control in the 1 and 3 ppm groups at termination, as well as in female 3 ppm recovery group animals. Although statistically significant in most instances, these findings were considered to be of no toxicological significance.
4.5	**Pathology**	No significant test substance-related adverse effects reported
4.6	**Histopathology**	No significant test substance-related adverse effects reported
4.7	**Other**	None

Section A6.9/02 Subchronic Neurotoxicity in Rats

Annex Point IIIA VI.1

Evaluation by Competent Authorities	
Date	2007/10/23
Materials and Methods	As presented above
Results and discussion	As presented above
Conclusion	NOAEL: 3 ppm (the highest dose tested), based on the absence of any test substance-related neurotoxic findings as well as any other relevant adverse effects
Reliability	2
Acceptability	Acceptable
Remarks	None
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.12 **Human Case Report**

Annex Point IIA6.9.1 *Medical surveillance data on manufacturing plant personnel*

Official use only

1 REFERENCE

1.1 Reference

Guth, Erhard (2003): Arbeitsmedizinische Betreuung von Mitarbeitern, die Phosphorwasserstoff exponiert sind (Translation: Occupational Health Care for Employees under Hydrogen Phosphide (PH_3) Exposition); IAS, Mannheim, Germany, April 23, 2003

2 GUIDELINES AND QUALITY ASSURANCE (NOT APPLICABLE)

3 MATERIALS AND METHODS

All workers involved with the production of Aluminium phosphide containing products are regularly monitored at intervals of 12 months. In this health inspection the following parameters are assessed:
- Overall health check-up, especially regarding skin alterations and nerve reflexes
- Hearing and vision test
- ECG
- Urinalysis
- Red blood count
- Leucocytes
- Thrombocytes
- Differential blood count
- Liver status parameters
- Creatinine
- Blood glucose

In intervals of 24 to 36 months x-ray investigations of the chest are carried out, additionally every working place is inspected.

4 RESULTS

The above-mentioned health examinations conducted with the plant personnel showed no negative health effects during the investigation period of 15 years.

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods see 3

5.2 Results and discussion see 4

5.3 Conclusion No negative health effects during the investigation period of 7 years

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	[redacted]
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	Applicant's version is adopted with the remark that the observation period was about 10 years.
Remarks	
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.12 **Human Case Report**

Annex Point IIA6.9.2 *Direct observation, e.g. clinical cases, poisoning incedents*

Official use only

1 REFERENCE

1.1 Reference

K. E. Zipf, Th. Arndt, R. Heintz (1967): Clinical Observation of a Case of Phostoxin Poisoning; Archiv für Toxikologie, Vol. 22, No.4 (Reprint, Translation

2 GUIDELINES AND QUALITY ASSURANCE (NOT APPLICABLE)

3 MATERIALS AND METHODS (NOT APPLICABLE)

4 SUBJECT

A detailed case report of aluminium phosphide poisoning: a 25-year-old gardener's labourer swallowed 6 Phostoxin tablets (70% aluminium phosphide and approximately 30% ammonium carbamate) dissolved in water, suicide attempt.

5 FINDINGS / CONCLUSION

Severe circulatory, cardiac and renal failure and liver damage resulted. Clearly apparent changes in ECG and EEG were found. The histological findings for liver and kidneys corresponded to a great extent with those stated in the literature, thus providing intra vitam confirmation.
One probable reason for the man having survived drinking a lethal dose of Phostoxin is that he immediately vomited the major portion of the poison. A further reason is that, due to the characteristic carbide odour, the nature of the poisoning could be recognised immediately and appropriate treatment commenced without delay.

The application of extracorporal haemodialysis and medication with heart and circulatory preparations contributed decisively towards prevention of a lethal course.

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	[redacted]
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Remarks	
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.12 **Human Case Report**

Annex Point IIA6.9.3 *Health records, both from industry and other available sources*

Official use only

1 REFERENCE

1.1 Reference

Barbosa, A.; et al. (1994): Evaluation of phosphine genotoxicity at occupational levels of exposure in New South Wales, Australia; Occup Environ Med 51, 700 - 705

2 GUIDELINES AND QUALITY ASSURANCE (NOT APPLICABLE)

3 MATERIALS AND METHODS

Study on 31 phosphine fumigators and 21 controls during the high fumigation season. All were volunteers and were evaluated for genotoxicity variables, including micronuclei in peripheral blood lymphocytes and urine mutagenicity. In parallel, all fumigators and 17 controls were evaluated for full haematology, multiple biochemical analysis, whole blood and serum cholinesterase activity.

4 RESULTS

The results for micronuclei showed no significant differences between fumigators and controls, but detected a strong association between age and increased frequency of micronuclei. Measurement of urine mutagenicity did not show any significant difference between fumigators and controls, but did show increased excretion of mutagens in smokers. All haematological and biochemical variables were within normal ranges, except for some non-specific changes in biochemistry.

At monitored occupational exposures of < 2.4 ppm/h our results show no association between phosphine exposure and genotoxic or toxicological effects in fumigators.

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

see 3

5.2 Results and discussion

see 4

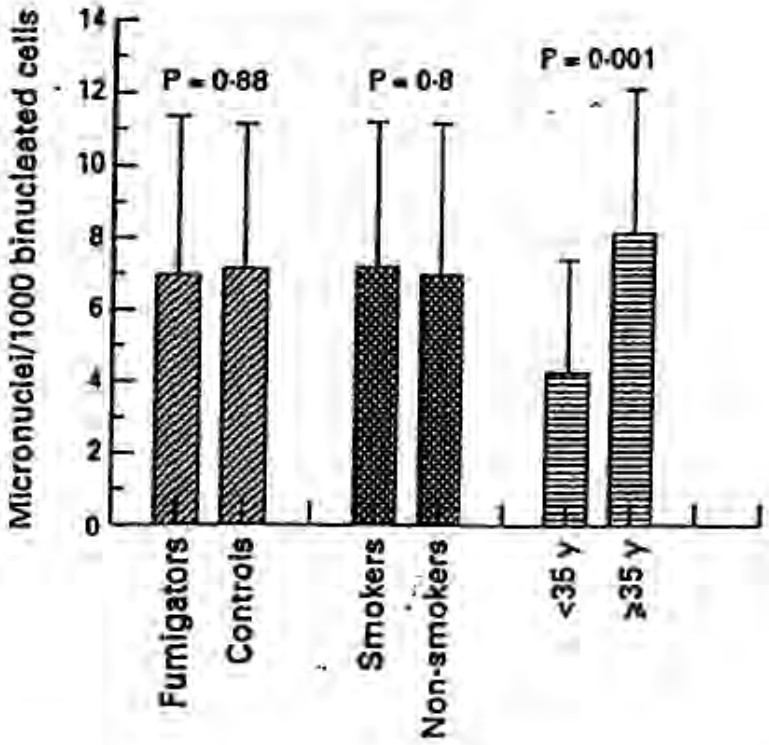
5.3 Conclusion

At monitored occupational exposures of < 2.4 ppm/h no association between phosphine exposure and genotoxic or toxicological effects in fumigators could be observed.

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	[redacted]
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Remarks	CA-Table A6.12.3.1 and A6.12.3.2 is added by CA
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Evaluation by Rapporteur Member State, CA-Tables

CA-Table IIA 6.12.3.1 Frequency in micronuclei (mean (SD)) in peripheral blood lymphocytes



Frequency of micronuclei (mean (SD)) in fumigators versus controls, smokers versus non-smokers and test persons under 35 years of age and 35 years of age and over compared by Wilcoxon test.

CA-Table IIA 6.12.3.2 Percentage of fumigators and controls with raised liver function variables

Liver variable	Normal range	Fumigators n = 71 (%)	Range	Controls n = 17 (%)	Range
Total bilirubin	3–18 μmol/l	2 (0·5)	19–21	0	—
Alkaline phosphatase	30–120 U/l	1 (1·0)	173	1 (5·5)	167
γ-Glutamyl transpeptidase	0–50 U/l	11 (15·5)	53–183	3 (27·3)	52–117
Alanine aminotransferase	0–45 U/l	4 (5·6)	47–156	2 (11·7)	48–71
Aspartate aminotransferase	0–45 U/l	1 (1·0)	47	0	—
≥ 1 Variable*		17 (24·0)	—	6 (35·3)	—

*Subjects with one or more raised liver function variables.

Section A6.12.3 Human Case Report

Annex Point IIA VI.6.9.3 *Health records, both from industry or other sources*

Official use only

		1 REFERENCE
1.1	**Reference**	Garry, VF; Griffith, J; Danzl, TJ; Nelson, RL; Whorton, EB; Krueger, LA, Cervenka, J (1989): Applicators and Phosphine; Science, Vol. 246: 251-255
		2 GUIDELINES AND QUALITY ASSURANCE (NOT APPLICABLE)
		3 MATERIALS AND METHODS
3.1	**Substance**	Phosphine as fumigant (or Phosphine and other pesticides)
3.2	**Persons exposed**	
3.2.1	Sex	not stated
3.2.2	Age/weight	not stated
3.2.3	Known Diseases	Persons with known diseases were excluded from the study
3.2.4	Number of persons	40 (9 exposed to Phosphine only)
3.2.5	Other information	no
3.3	**Exposure**	Inhalation
3.3.1	Reason of exposure	occupational
3.3.2	Frequency of exposure	multiple
3.3.3	Overall time period of exposure	Application season (time period not specified)
3.3.4	Duration of single exposure	not stated
3.3.5	Exposure concentration/dose	Measured in the breathing zone: Workers involved in enclosed space application (grain bin), exposures ranged from 0.4 to 5.8 mg/m³ (n= 10) with a mean on 2.97 mg/m³. Phosphine release from the phosphide occurred in some instances in as little as 5 min. Among workers involved in open air application (rail car), exposure ranged from 0.1 to 0.90 mg/m³ (n=4).
3.3.6	Other information	
3.4	**Examinations**	100 metaphase lymphocytes from each sample were analyzed to detect gaps, deletion, breaks, or other aberrations.
3.5	**Treatment**	n. a.
3.6	**Remarks**	
		4 RESULTS
4.1	**Clinical Signs**	no

Section A6.12.3 Human Case Report

Annex Point IIA VI.6.9.3 *Health records, both from industry or other sources*

4.2	**Results of examinations**	Examinated workers had significantly increased stable chromosome rearrangements, primarily translocations in G-banded lymphocytes. Less stable aberrations including chromatid deletions and gaps were significantly increased only during the application season, but not at this later time point.
4.3	**Effectivity of medical treatment**	no medical treatment
4.4	**Outcome**	n. a.
4.5	**Other**	n. a.

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	Human Genotoxicity Test
5.2	**Results and discussion**	see 4.2
5.3	**Conclusion**	We consider this study as not useful to assess the genotoxicity of Phosphine in humans for the following reasons: 1. The study has been conducted with a very small sample of workers who are exposed to phosphine "alone" (n=9), all other workers had been exposed to PH3 and other pesticides and symptoms therefore can not be directly related to Phosphine. Barbosa et al. who examined a greater group of fumigators (n = 31) did not find any association between phosphine exposure and genotoxic effects. 2. In this article it is said that control subjects were matched for age, sex and smoking habits, but in the evaluation of the data these factors are not taken into account. Smoking has a much higher influence on mutation frequency than Phosphine (Barbosa et al., 1994, IIIA 6.12.3) and DNA damage increases with age. All these factors are not considered in the evaluation of the data. 3. A second examination of the workers (6 weeks to 3 months later) showed no difference between the nonbanded 48-hours cultures from workers exposed weeks to months earlier and concurrent controls. The author itself states, that whether the chromosome rearrangements they observed are a specific effect of phosphine is uncertain at the time of the study (1989) and studies (in vitro and in vivo) on genotoxicity which were conducted later could not confirm the results of Gary et al.

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	[redacted]
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Remarks	
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.12 **Annex Point IIA6.9.4**	**Epidemiological studies on the general population**	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA *As outlined in the TNsG on data requirements, the applicant must always be able to justify the suggested exemptions from the data requirements. The justifications are to be included in the respective location (section) of the dossier.* *If one of the following reasons is marked, detailed justification has to be given below. General arguments are not acceptable*	Official use only
Other existing data [ ] **Limited exposure [ ]**	**Technically not feasible [ ]** **Scientifically unjustified [ ]** **Other justification [X]**	
Detailed justification: [redacted] [redacted]		
Undertaking of intended data submission [ ]	*Give date on which the data will be handed in later (Only acceptable if test or study is already being conducted and the responsible CA has agreed on the delayed data submission.)*	
	Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	[redacted]	
Evaluation of applicant's justification	[redacted]	
Conclusion	[redacted]	
Remarks		
	COMMENTS FROM OTHER MEMBER STATE *(specify)*	
Date	*Give date of comments submitted*	
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*	
Conclusion	*Discuss if deviating from view of rapporteur member state*	
Remarks		

Section A6.12 **Human Case Report**

Annex Point IIA6.9.5 *Diagnosis of poisoning including specific signs of poisoning and clinical tests Diagnosis of poisoning including specific signs of poisoning and clinical tests*

Official use only

1 REFERENCE

1.1 Reference

Chugh, S.N.; et al. (1991): Incidence & outcome of aluminium phosphide poisoning in a hospital study; Indian J Med Res [B] 94, June 1991, pp 232 - 235

2 GUIDELINES AND QUALITY ASSURANCE (NOT APPLICABLE)

3 SUBJECT

A total of 418 patients with aluminium phosphide poisoning admitted during January 1981 to December 1987, were studied and analysed for various parameters. The patients showed varied clinical features as shown in the following table:

	No. of patients	%
Gastrointestinal upset, nausea, epigastric burning, retching, pain, etc.	381	91.2
Clear mentation with restlessness, anxiety at admission	381	91.2
Shock	376	90.0
Signs of sympathetic overactivity (sweating, tachycardia)	278	66.5
Oliguria	214	51.2
Tachypnoea, dyspnoea, crepts and rhonchi	192	45.8
Acute renal failure (raised urea and NPN and serum creatinine etc.)	32	7.6
Hepato-biliary (tender hepatomegaly, raised SGOT/SGPT; jaundice)	18	4.3
Bradycardia	14	3.3

All patients were treated similarly with dopamine infusion (starting dose 4 – 8 µg/kg/min), intravenous glucose drip (2 – 3 l glucose saline in first 4 – 6 h), continuous O_2 administration, and systemic corticosteroids. Frequent electrocardiographic monitoring showed varied pattern of ST-T changes, conduction and rhythm disturbances (see following table).

ECG abnormalities (160 patients)	38.2%
ST-T changes (elevation or depression) in more than 2 leads	56
SVT	
Varied sino-atrial conduction (sino-atrial block, sinus pauses)	20
Atrial fibrillation or strial premature beats	14
Bradycardia	14
Bundle branch block: LBBB	6
RBBB	4
Ventricular tachycardia	3
Paricarditis (elevation with ST-T upwards)	3

Section A6.12 **Human Case Report**

Annex Point IIA6.9.5 *Diagnosis of poisoning including specific signs of poisoning and clinical tests Diagnosis of poisoning including specific signs of poisoning and clinical tests*

4 RESULTS

The above-mentioned health examinations conducted with the plant personnel showed no negative health effects during the investigation period of 7 years.

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	Hospital study on aluminium phosphide poisoning
5.2	**Results and discussion**	see above
5.3	**Conclusion**	The mortality was high and directly related to the dose of poison consumed. The bad prognostic indices and presence of complications further increased the mortality. The mortality did not have any relation with duration and time interval between ingestion and admission.

Evaluation by Competent Authorities

EVALUATION BY RAPPORTEUR MEMBER STATE

Date	[redacted]
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Remarks	CA-Table A6.12.5.1 and A6.12.5.2 were added by the RMS.

COMMENTS FROM ... *(specify)*

Date	*Give date of comments submitted*
Materials and Methods	*Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*

Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Evaluation by Rapporteur Member State, CA-Tables

CA-Table IIA6.12.5.1 Clinical spectrum of aluminium phosphide poisoning

	No. of patients	%
Gastrointestinal upset, nausea, epigastric burning, retching, pain etc	381	91.2
Clear sensation with restlessness, anxiety at admission	381	91.2
Shock	376	90.0
Signs of sympathetic overactivity (sweating, tachycardia)	278	66.5
Oliguria	214	51.2
Tachypnoea, dyspnoea, crepts and rhonchi	192	45.8
Acute renal failure (raised urea and NPN and serum creatinine etc)	32	7.6
Hepato-biliary (tender hepatomegaly, raised SGOT/SGPT; jaundice)	18	4.3
Bradycardia	14	3.3

CA-Table IIA6.12.5.2 Electrocardiographic changes

Table IV. Electrocardiographic changes	
ECG abnormalities (160 patients)	38.2%
ST-T changes (elevation or depression) in more than 2 leads	56
SVT	
Varied sino-atrial conduction (sino-atrial block, sinus pause)	30
Atrial fibrillation or atrial premature beats	14
Bradycardia	14
Bundle branch block : LBBB	6
RBBB	4
Ventricular tachycardia	3
Pericarditis (elevation with ST-T upwards)	3

Section A6.12 Annex Point 6.9.6	Sensitisation/allergenicity observations	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA *As outlined in the TNsG on data requirements, the applicant must always be able to justify the suggested exemptions from the data requirements. The justifications are to be included in the respective location (section) of the dossier.* *If one of the following reasons is marked, detailed justification has to be given below. General arguments are not acceptable*	Official use only
Other existing data [ ] **Limited exposure [ ]**	**Technically not feasible [ ]** **Scientifically unjustified [ ]** **Other justification [X]**	
Detailed justification: [redacted]		
Undertaking of intended data submission [ ]	*Give date on which the data will be handed in later (Only acceptable if test or study is already being conducted and the responsible CA has agreed on the delayed data submission.)*	
	Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	[redacted]	
Evaluation of applicant's justification	[redacted]	
Conclusion	[redacted]	
Remarks		
	COMMENTS FROM OTHER MEMBER STATE *(specify)*	
Date	*Give date of comments submitted*	
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*	
Conclusion	*Discuss if deviating from view of rapporteur member state*	
Remarks		

Section A6.12 **Human Case Report**

Annex Point IIA6.9.7 *Specific treatment in case of an accident of poisoning: first aid measures, antidotes and medical treatment*

Official use only

1 REFERENCE

1.1 References

D. Weller (1982): Toxicology of Hydrogen Phosphide (Phosphine) Therapy of Poisoning, Degesch GmbH, Frankfurt, Germany
L. Benzing (1992): Erste Hilfe und Therapiemaßnahmen, Verlag Alfred Strothe, Germany
Detia-Degesch GmbH (2003) EC-Safety Data Sheet, Laudenbach, Germany

2 GUIDELINES AND QUALITY ASSURANCE (NOT APPLICABLE)

3 MATERIALS AND METHODS

First aid

Inhalation exposure:

(1) Move victims to fresh air in case of headache, dizziness, feeling of constriction, difficult breathing and/or nausea, consult a physician.
(2) Emergency personnel should avoid self-exposure
(3) Remove contaminated clothes
(4) Place victim on side if unconscious. Stay with victim and check his state of health even if he feels "healthy"
(5) Keep victim quiet, warm and comfortable.
(6) Victim should inhale a dexamethason (Auxiloson) spray
(7) Victim should always be accompanied to hospital or to physician

Dermal exposure:

(1) Remove any rests by brushing; only then use water for cleansing (in addition to the above mentioned points).

Eye contact:

(1) Remove rests of preparation with fluff-free cloth; rinse with plenty of water and apply eye drops only after no more powdery residues are visible (in addition to the above mentioned points).

Special aids required for First Aid measures:

(1) Have methyl prednisolon (application by physician) and a dexamethason spray available

Therapeutic regimes

Cortison: Methyl prednisolon first 1000 mg i.v. and i.m.
Inhalation of Auxilon spray
Treatment with Cystein (Reducdyn) i.v. and per os
In case of convulsions Diazepam
Symptomatic treatment
Correction of fluid loss and electrolyte disturbance
Dialysis, if the quantity of swallowed/inhaled Metal phosphide/Phosphine is not known

Section A6.12 **Human Case Report**

Annex Point IIA6.9.7 *Specific treatment in case of an accident of poisoning: first aid measures, antidotes and medical treatment*

4 RESULTS
(NOT APPLICABLE)

5 APPLICANT'S SUMMARY AND CONCLUSION
(NOT APPLICABLE)

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	[redacted]
Materials and Methods	[redacted]
Results and discussion	
Conclusion	[redacted]
Remarks	
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.12 **Human Case Report**

Annex Point IIA6.9.8 *Prognosis following poisoning*

Official use only

1 REFERENCE

1.1 Reference

Misra, U.K.; et al. (1988): Acute Phosphine Poisoning following Ingestion of Aluminium Phosphide, Human Toxicol., 7, 343 - 354

2 GUIDELINES AND QUALITY ASSURANCE (NOT APPLICABLE)

3 MATERIALS AND METHODS

Eight cases of phosphine poisoning following ingestion of aluminium phosphide tablets for suicidal attempt are described. The clinical picture consisted of gastritis, altered sensorium and peripheral vascular failure in all cases, cardiac arrhytmia (3), jaundice and renal failure (1 each). Six patients died, the mean hospital stay was 19 h (range 4 – 72). Post-mortem examination was performed in two patients, revealing pulmonary oedema, gastrointestinal mucosal congestion, petechial haemorrahages on the surface of liver and brain. Histopathological changes included pulmonary oedma, desquamation of the lining epithelium of the bronchioles; vascuolar degeneration of hepatocytes, dilatation and engorgement of hepatic central veins, sinusoids and areas showing nuclear fragmentation.
The following table summarizes the clinical picture of oral aluminium phosphide poisoning patients:

Patient no.	Age/Sex	No. of tablets taken	Clinical features	Remarks
1	14/F	1	Gastritis, breathing difficulty, PVF**	Discharged Day 2
2*	31/M	2	Vomiting, coma, PVF**	Died 22 h
3	19/M	0.5	Gastritis, PVF**	Discharged Day 5
4*	26/M	20	Vomiting, drowsy, PVF**	Died 5.5 h
5	25/M	4	Vomiting, drowsy	Died 2 h
6	25/M	2	Vomiting, unconscious	Died 2 h
7	24/F	?	Vomiting, unconscious	Died 5.5 h
8	20/F	3	Vomiting, delirium, PVF**, renal failure, jaundice, ventricular tachycardia	Died 72 h

* subjected to autopsy
** peripheral vascular failure

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	[redacted]
Materials and Methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Remarks	CA-Table A6.12.8 was added by RMS.
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Evaluation by Rapporteur Member State, CA-Tables

CA-Table IIA6.12.8 Clinical summary of oral aluminium phosphide poisoning patients

Table 1 Clinical summary of oral aluminium phosphide poisoning patients

Patient no.	Age/sex	No. of tablets taken	Clinical features	Remarks
1	16F	1	Gastritis, breathing difficulty, PVF	Discharged day 2
2*	31M	2	Vomiting, coma, PVF	Died 22 h
3	19M	0.5	Gastritis, PVF	Discharged day 5
4	26M	20	Vomiting, drowsy, PVF	Died 5.5 h
5	25M	4	Vomiting, drowsy	Died 1 h
6	28M	2	Vomiting, unconscious	Died 3 h
7	24F	4	Vomiting, unconscious	Died 5.5 h
8	20F	3	Vomiting, delirium, PVF, renal failure, jaundice, ventricular tachycardia	Died 72 h

* Subjected to autopsy.
PVF-peripheral vascular failure.

Section A6.13 Annex Point IIIA-IV.2	Toxic effects on livestock and pets	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ]	**Technically not feasible [ ]** **Scientifically unjustified [ ]**	
Limited exposure [X]	**Other justification [ ]**	
Detailed justification:	[redacted]	
Undertaking of intended data submission [ ]		
	Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	[redacted]	
Evaluation of applicant's justification	[redacted]	
Conclusion	[redacted]	
Remarks		
	COMMENTS FROM OTHER MEMBER STATE *(specify)*	
Date	*Give date of comments submitted*	
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*	
Conclusion	*Discuss if deviating from view of rapporteur member state*	
Remarks		

Section A6.14 Other test(s) related to the exposure of humans

Annex Point IIA VI.6.9

Official use only

		1 REFERENCE
1.1	**Reference**	Garry, VF; Harkins, ME; Erickson, LL; Long-Simpson, LK; Holland, SE; Burroughs, BL (2002): Birth Defects, Season of Conception, and Sex of Children Born to Pesticide Applicators Living in the Red River Valley of Minnesota, USA; Environmental Health Perspectives, Vol. 110: 441-449.
		2 GUIDELINES AND QUALITY ASSURANCE (NOT APPLICABLE)
		3 MATERIALS AND METHODS
3.1	**Substance**	Different pesticides, among these phosphine
3.2	**Persons exposed**	
3.2.1	Sex	male
3.2.2	Age/weight	not stated
3.2.3	Known Diseases	not stated
3.2.4	Number of persons	536 children fathered by pesticide applicators
3.2.5	Other information	no
3.3	**Exposure**	not specified (for phosphine: inhalation)
3.3.1	Reason of exposure	occupational
3.3.2	Frequency of exposure	not specified
3.3.3	Overall time period of exposure	not specified
3.3.4	Duration of single exposure	not specified
3.3.5	Exposure concentration/dose	not specified
3.3.6	Other information	
3.4	**Examinations**	Statistical evaluation of birth defects, adverse developmental effects of children, sex of children
3.5	**Treatment**	no medical treatment
3.6	**Remarks**	
		4 RESULTS
4.1	**Clinical Signs**	see 4.2
4.2	**Results of examinations**	For phosphine: Adverse neurologic and neurobehavioral developmental effects clustered among the children born to applicators of the fumigant phosphine (odds ratio [OR] = 2.48; confidence interval [CI], 1.2-5.1).

Section A6.14 Other test(s) related to the exposure of humans

Annex Point IIA VI.6.9

4.3	**Effectivity of medical treatment**	no medical treatment
4.4	**Outcome**	n. a.
4.5	**Other**	n. a.

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	Statistical evaluation of birth defects of children fathered by pesticide applicators.
5.2	**Results and discussion**	see 4.2 and 5.3
5.3	**Conclusion**	We consider this study as not useful to assess the teratogenicity of Phosphine in humans for the following reasons: 1. The article in question is on children of farm families with parent-reported birth defects. Since the fathers are as farmers involved in application of different pesticides it is not possible to relate the effects directly to phosphine. 2. No information about the kind of application is given (e.g. concentrations or if PPE is used or not). 3. The authors report that they have previously demonstrated that the frequency of birth defects among children of residents of the Red River Valley (RRV), Minnesota, USA, was significantly higher than in other major agricultural regions. Nevertheless they do not consider other factors as reason for these birth defects but focus only on the use of pesticides. Additionally, the authors do not compare birth-defects of farm families with other non-farmer residents of this region. 4. The study bases on parent-reported information only (telephone interviews and written questionnaire), no medical examination has been conducted.

Evaluation by Competent Authorities

EVALUATION BY RAPPORTEUR MEMBER STATE

Date	[redacted]
Materials and methods	[redacted]
Results and discussion	[redacted]
Conclusion	[redacted]
Remarks	

COMMENTS FROM ... *(specify)*

Date	*Give date of comments submitted*
Materials and Methods	*Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.14 Annex Point IIIA-XI.2	Other test(s) related to the exposure of humans	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ]	**Technically not feasible** [ ] **Scientifically unjustified** [ ]	
Limited exposure [X]	**Other justification** [ ]	
Detailed justification:		
[redacted]		
Undertaking of intended data submission [ ]		
	Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	[redacted]	
Evaluation of applicant's justification	[redacted]	
Conclusion	[redacted]	
Remarks		
	COMMENTS FROM OTHER MEMBER STATE *(specify)*	
Date	*Give date of comments submitted*	
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*	
Conclusion	*Discuss if deviating from view of rapporteur member state*	
Remarks		

Section A6.15.1/6.15.2

Annex Point IIIAXI.1

Identification and behaviour of the residues of the active substance

Official use only

[redacted]

Section A6.15.1/6.15.2
Annex Point IIIAXI.1

Identification and behaviour of the residues of the active substance

[redacted]

[redacted] Entomol. Zool. 9, 127-132

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	[redacted]
Materials and Methods	[redacted]
Results and discussion	Acceptable
Conclusion	[redacted] Residues in food or feed are not expected as a result of the proposed use.
Remarks	[redacted]
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.15.3
Annex Point IIIAXI.1

Estimation of potential or actual exposure of the active substance to humans through diet and other means

Official use only

[redacted]

[redacted]

Reference 6.15.3/01: [redacted] Aluminium and Magnesium Phosphide / Phosphine Gas – Deduction of Reference Figures (ARfD and ADI) for the Consumer Risk Assessment, [redacted]

Reference 6.15.3/02: [redacted] Products Generating Hydrogen Phosphide – Calculation of the Theoretical Maximum Daily Intake (TMDI), [redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	[redacted]
Materials and Methods	[redacted]
Results and discussion	Acceptable.
Conclusion	[redacted] Residues in food or feed are not expected as a result of the proposed use.
Remarks	
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.15.4

Annex Point IIIA-XI.1.7

Proposed acceptable residues and the justification of their acceptability

Official use only

[redacted]

[redacted]

Unprocessed cereals 0.1 mg/kg
Other agricultural commodities 0.01 mg/kg

[redacted]

[redacted]

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	[redacted]
Materials and Methods	[redacted]
Results and discussion	Acceptable.
Conclusion	[redacted] Residues in food or feed are not expected as a result of the proposed use.
Remarks	
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	