BACTERIAL RESISTANCE TO IODINE BASED DISINFECTANTS

A REVIEW

CHART 1: RELEVANCE OF REFERENCES SITED FOR IODINE RESISTANCE

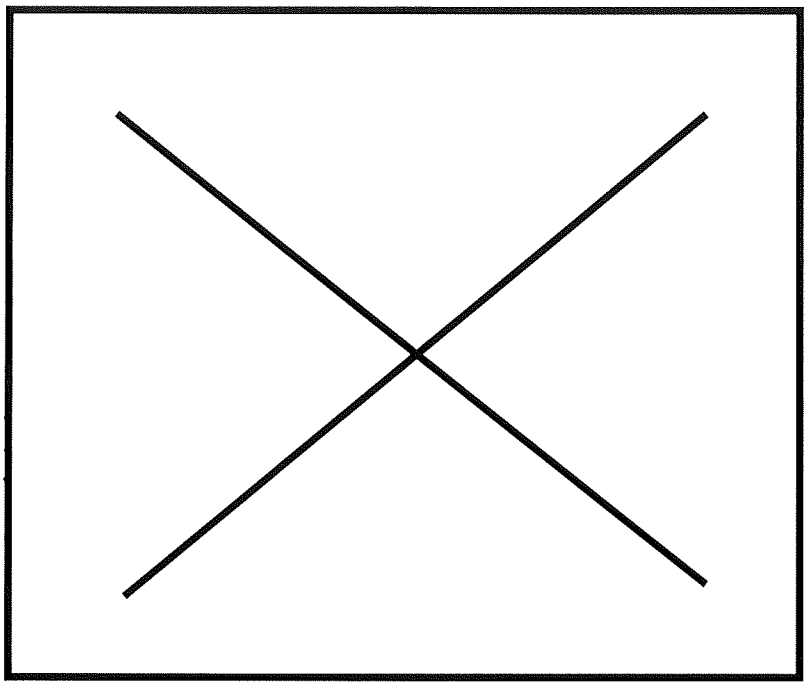
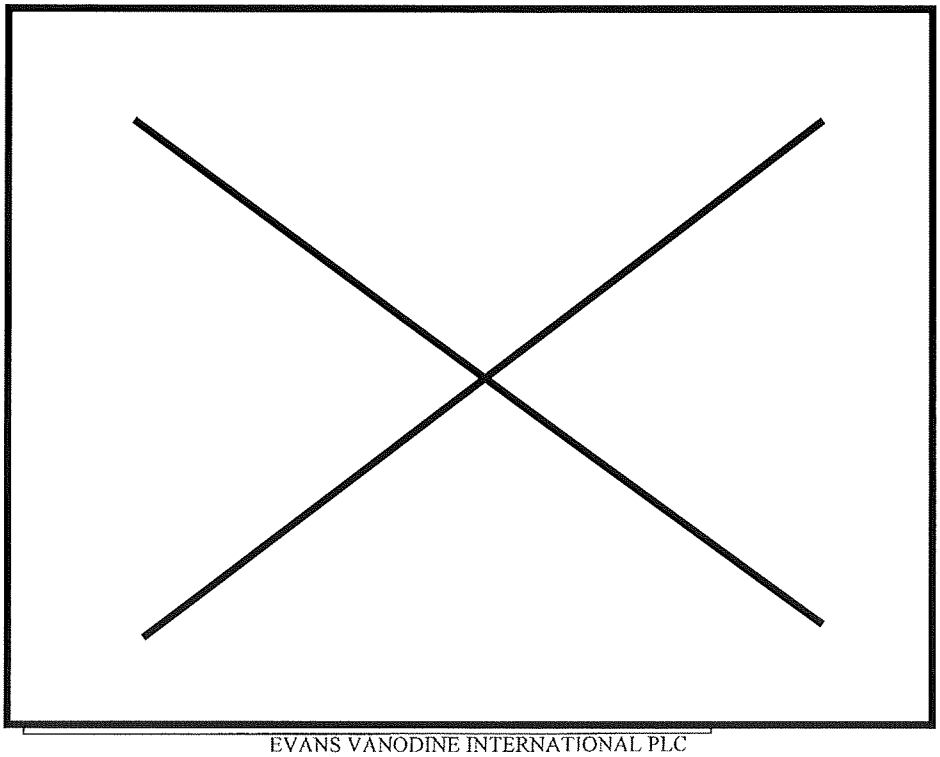
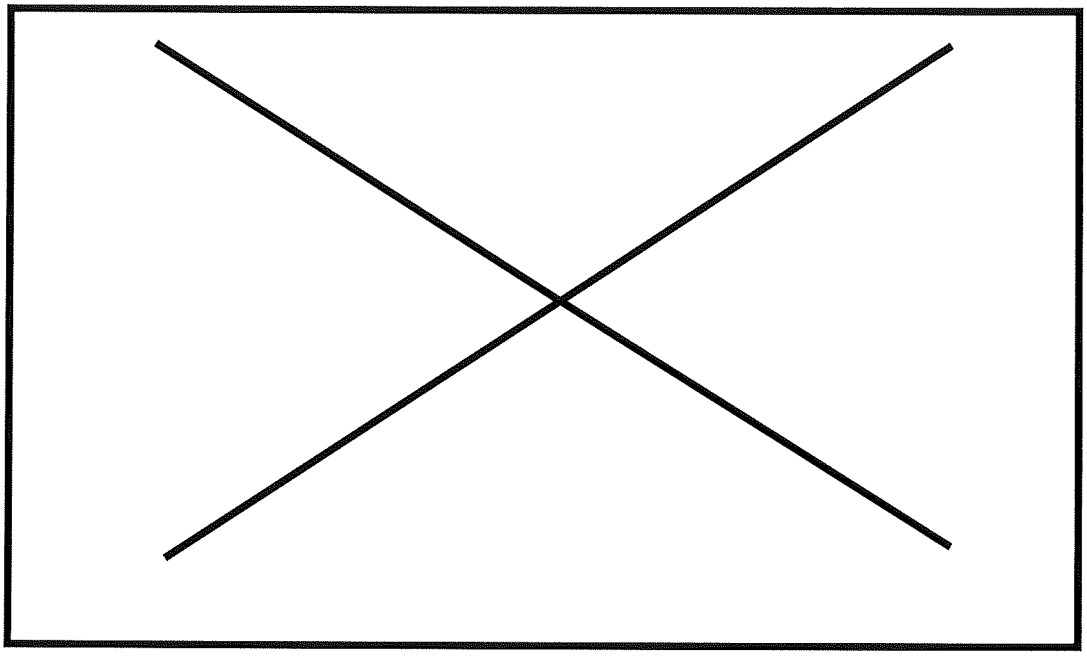


CHART 2: CATERGORIES OF REFERENCES FOR IODINE RESISTANCE



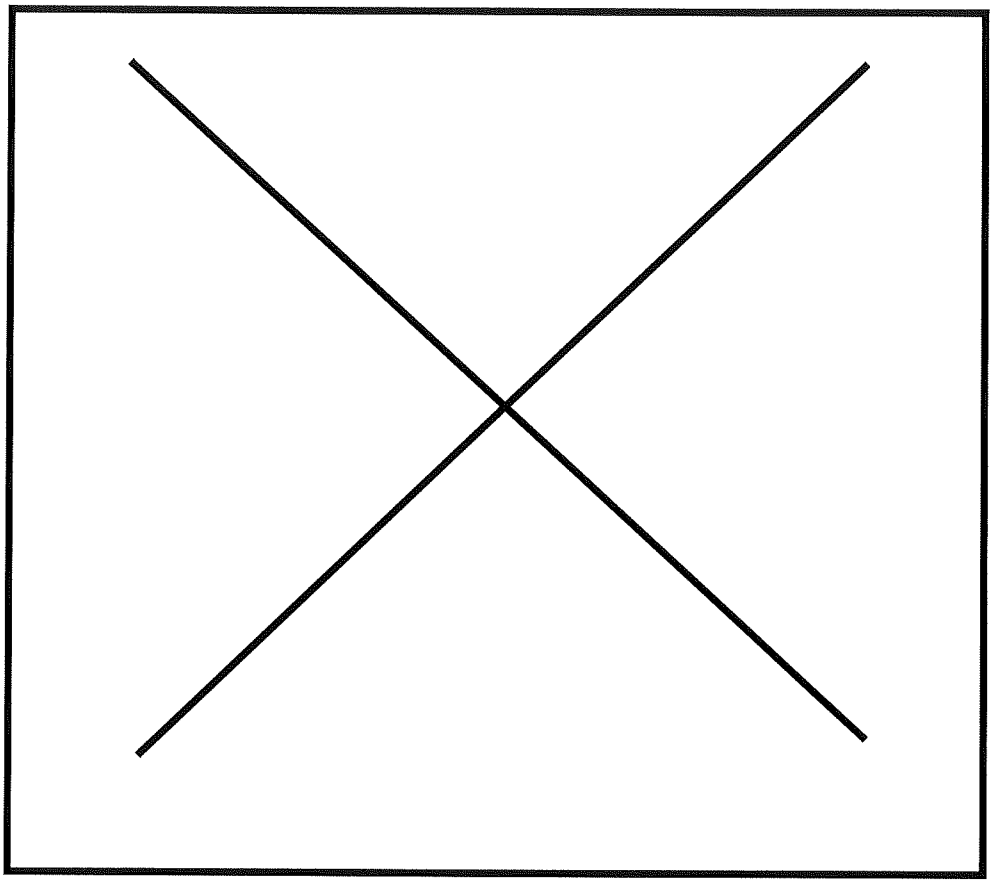
BACTERIAL RESISTANCE TO IODINE BASED DISINFECTANTS
A REVIEW

CHART 3: Somatic cell counts in England and Wales



BACTERIAL RESISTANCE TO IODINE BASED DISINFECTANTS
A REVIEW

CHART 4: PERCENTAGE OF TEAT DISINFECTANTS USED GLOBALLY



BACTERIAL RESISTANCE TO IODINE BASED DISINFECTANTS
A REVIEW

REFERENCES

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BACTERIAL RESISTANCE TO IODINE BASED DISINFECTANTS

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Competent Authority Report

Work Programme for Review of Active Substances in Biocidal Products Pursuant to Council Directive 98/8/EC

IODINE (PT1, PT3, PT4, PT22)

DOCUMENT III-A6

Toxicology and metabolism

Rapporteur Member State: Sweden

Draft Final May 2013

KEMI
Kemikalieinspektionen
Swedish Chemicals Agency

Table of contents:

Section A6.1.1/01-06 Acute Toxicity (oral)

Annex Point IIA VI.6.1.1

[redacted]

Official use only

1. REFERENCE

1.1 Reference

[1] Hazardous Substance Data Bank (HSDB), p. 12
Doc. No. 591-004 (published); Section A6.1.1/01

[2] Lewis, R.J. (1992): Sax's Dangerous Properties of Industrial Materials. 8th ed. Volumes 1-3. New York, NY: Van Nostrand Reinhold
Doc. No. 592-054 (published); Section A6.1.1/02

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Doc. No. 592-035 (published); Section A6.1.1/03

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Doc. No. 592-018 (published); Section A6.1.1/04

[5] Registry of Toxic Effects of Chemical Substances (RTECS), p. 3
Doc. No. 591-002 (published); Section A6.1.1/05

[6] California Environmental Protection Agency, Department of Pesticide Regulation, Medical Toxicology Branch (2005), Summary of Toxicology Data, Iodine and related Iodine Complexes, p. 2
http://www.cdpr.ca.gov/docs/toxsums/pdfs/718c.pdf
Doc. No. 581-013 (published); Section A6.1.1/06

1.2 Data protection [redacted]

1.2.1 Data owner [redacted]

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 Not applicable. [redacted] X1

2.2 GLP [redacted]

2.3 Deviations Not applicable

3 MATERIALS AND METHODS

3.2 Test material Iodine [redacted]

3.3 Test method [redacted]

3.4 Administration/ Exposure [redacted]intravenous or oral

3.4.1 Administration rate [redacted]

Section A6.1.1/01-06 Acute Toxicity (oral)

Annex Point IIA VI.6.1.1

---

4 RESULTS AND DISCUSSION

4.2 LD_{50}

[redacted]

- LD_{50} Rat oral 14 g/kg bw [redacted]

[redacted]

LD_{50} Mouse oral 22 g/kg bw [redacted]

[redacted]

[redacted]

LD_{50} (i.v.) in the dog of 17 g/kg bw [redacted]

4.3 LD_0

[redacted]

- LD_0 Dog oral 0.8 g/kg bw

4.4 Others

[redacted]

5 APPLICANT'S SUMMARY AND CONCLUSION

5.2 Materials and methods

[redacted]

5.3 Results and discussion

[redacted]

Section A6.1.1/01-06 Acute Toxicity (oral)

Annex Point IIA VI.6.1.1

5.4	**Conclusion**	The results of acute oral toxicity studies performed in animals demonstrate only a very low acute toxicity potential following oral administration. Iodine has not to be classified and labelled with respect to acute oral toxicity.
5.4.1	Reliability	[redacted]
5.4.2	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]

Section A6.1.2/01 Acute Toxicity (dermal)

Annex Point IIA, VI6.1.2

[redacted]

Official use only

1 REFERENCE

1.1	**Reference**	ESIS: European chemical Substances Information System; Doc. No. 991-003 (published); Section A6.1.2/01
1.2	**Data protection**	[redacted]
1.2.1	Data owner	[redacted]
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**	Not applicable [redacted]
2.2	**GLP**	Not applicable [redacted]
2.3	**Deviations**	Not applicable [redacted]

3 MATERIALS AND METHODS

3.2	**Test material**	Iodine [redacted]
3.3	**Test method**	Not applicable [redacted]
3.4	**Classification under EU Directive 67/548/EEC**	Iodine is classified under EU Directive 67/548/EEC as being harmful via dermal exposure, expressed by the respective risk phrase R21 "Harmful in contact with skin". Please refer also to Section A9/01 (Classification and Labelling). Thus, the LD_{50} dermal (rat or rabbit) has to be $400 < LD_{50} \leq 2000$ mg/kg.

[redacted]

4 RESULTS AND DISCUSSION

4.2	**LD_{50}**	LD_{50} dermal (rat or rabbit) has to be $400 < LD_{50} \leq 2000$ mg/kg.

5 APPLICANT'S SUMMARY AND CONCLUSION

5.2	Materials and methods	[redacted]

Section A6.1.2/01 Acute Toxicity (dermal)

Annex Point IIA, VI6.1.2

5.3	**Results and discussion**	Iodine is classified as being harmful via dermal exposure. Thus, the LD_{50} dermal (rat or rabbit) has to be $400 < LD_{50} \square < 2000$ mg/kg.
		[redacted]
5.4	**Conclusion**	Iodine is classified as being harmful via dermal exposure.
5.4.1	Reliability	[redacted]
5.4.2	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]

Section A6.1.3/01-08 Acute Toxicity (inhalation)

Annex Point IIA VI.6.1.3

[redacted]

Official use only

1 REFERENCE

1.1 Reference

[1] ESIS: European chemical Substances Information System
Doc. No. 991-003 (published); Section A6.1.3/01

[2] Lewis, R.J. (1992): Sax's Dangerous Properties of Industrial Materials. 8th ed. Volumes 1-3. New York, NY: Van Nostrand Reinhold, p. 1988
Doc. No. 592-054 (published); Section A6.1.3/02

[3] Registry of Toxic Effects of Chemical Substances (RTECS),
p. 2
Doc. No. 591-002 (published); Section A6.1.3/03

[4] Flury F., Zernik F. (1931): Schädliche Gase, Dämpfe, Nebel, Rauch und Staubarten (Harmful Gases, Vapours, Mists, Fume and Dust Types). Berlin, Germany. Julius Springer Verlag,
p. 123 - 124
Doc. No. 592-068 (published); Section A6.1.3/04

[5] Data base search on Iodine, p. 20-21 and p. 15
Doc. No. 091-001 (published), Section A6.1.3/05

[6] IDLH (Immediately Dangerous to Life and Health), p. 1-2
Doc. No. 592-035 (published); Section A6.1.3/06

[7] Toxikologisch-arbeitsmedizinische Begründung von MAK-Werten; DFG Evaluation for MAK Values; The MAK-Collection for Occupational Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area; ISBN 3-527-19030-9
Doc. No. 592-051 (published); Section A6.1.3/07

[8] Hazardous Substance Data Bank (HSDB), pp. 5, 7, 12, 20:
Doc. No. 591-004 (published); Section A6.1.3/08

1.2 Data protection [redacted]

1.2.1 Data owner [redacted]

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 Not applicable. [redacted]

2.2 GLP [redacted]

2.3 Deviations Not applicable

3 MATERIALS AND METHODS

Section A6.1.5/01 Skin sensitisation

Annex Point IIA VI.6.1.5

Guinea pig maximisation test (GPMT)

Official use only

1 REFERENCE

1.1	**Reference**	[redacted] (2002): Iodine: Skin Sensitisation in the Guinea Pig – Magnussen and Kligman Maximisation Method. [redacted]
1.2	**Data protection**	[redacted]
1.2.1	Data owner	[redacted]
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] Directive 96/54/EC, B.6
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	Preparation of test substance for application	[redacted]
3.1.2.5	Pre-test performed on irritant effects	[redacted]
3.2	**Test Animals**	
3.2.1	Species	Guinea pigs
3.2.2	Strain	Albino Dunkin Hartley
3.2.3	Source	[redacted]
3.2.4	Sex	male
3.2.5	Age/weight at study initiation	[redacted]

Section A6.1.3/01-08 Acute Toxicity (inhalation)

Annex Point IIA VI.6.1.3

3.1	**Test material**	Iodine [redacted]
3.2	**Test method**	Not applicable, [redacted]

4 RESULTS AND DISCUSSION

4.1 **LC_{50}**

Iodine is classified under EU Directive 67/548/EEC as being harmful via inhalation, expressed by the respective risk phrase R20 "Harmful by inhalation[redacted]

Thus, it can be concluded that if vapour or gas is inhaled the

LC_{50} (rat) is $2 < LC_{50} \leq 10$ mg/L/4h

and if aerosols and dust is inhaled, the

LC_{50} (rat) is $1 < LC_{50} \leq 5$ mg/L/4h

4.2 **LC_0**

[redacted]

LC_{Lo} (inh-rat): 800 mg/m^3/1h
The LC_{Lo} value is equivalent to 76 ppm

[redacted]

LC_{Lo} (inh-rat): 137 ppm/m^3/1h

Section A6.1.3/01-08 Acute Toxicity (inhalation)

Annex Point IIA VI.6.1.3

4.3 Other study results and information

[redacted]

- Immediately Dangerous to Life or Health (IDLH): 2 ppm

[redacted]

The IDLH is equivalent to 21 mg/ m^3.

- Irritating concentration: 2.0 mg/m^3

[redacted]

The irritating concentration is equivalent to 0.19 ppm.

This value is confirmed by reports that "work was possible with out any irritation at 0.1 ppm and difficult but possible at 0.15 to 0.2 ppm and that work was impossible at 0.3 ppm", [redacted]

[redacted] An occupational exposure limit value (STEL; MAK; TWA; CEILING; TLV) of 0.1 ppm or 1 mg/m^3 has been established for Iodine at the working place [redacted]

-

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

[redacted]

5.2 Results and discussion

[redacted]

Section A6.1.3/01-08 Acute Toxicity (inhalation)

Annex Point IIA VI.6.1.3

5.3	**Conclusion**	Iodine is a strong irritant to the upper respiratory system and due to this also evaluated as harmful via inhalation.
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]

Section A6.1.4.1/01-04 Acute Eye Irritation

Annex Point IIA VI.6.1.4

			Official use only
		1 REFERENCE	
1.1	**Reference**	[1] Hazardous Substance Data Bank (HSDB), pp. 5, 7, 12, 20: Doc. No. 591-004 (published); Section A6.1.4.1/01	
		[2] INCHEM: Poison Information Monograph on Iodine (PIM 280), p. 8 (p. 51 of the whole document 591-008) http://www.inchem.org/documents/pims/pharm/iodine.htm Doc. No. 591-008 (published); Section A6.1.4.1/02	
		[3] GESTIS-database on hazardous substances of the German institutions for statutory accident insurance and prevention ("Berufsgenossenschaften"), p. 2 www.hvbg.de/bgia/gestis-database Doc. No. 592-050 (published); Section A6.1.4.1/03	
		[4] ESIS: European chemical Substances Information System Doc. No. 991-003 (published); Section A6.1.4.1/04	
1.2	**Data protection**	[redacted]	
1.2.1	Data owner	[redacted]	
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**	Not applicable. [redacted]	
2.2	**GLP**	Not applicable. [redacted]	
2.3	**Deviations**	Not applicable	
		3 MATERIALS AND METHODS	
3.2	**Test material**	Iodine [redacted]	
3.3	**Test method**	Not applicable. [redacted]	

Section A6.1.4.1/01-04 Acute Eye Irritation

Annex Point IIA VI.6.1.4

4 RESULTS AND DISCUSSION

4.2 Results

[redacted]

4.3 Discussion

[redacted]

5 APPLICANT'S SUMMARY AND CONCLUSION

5.2 Materials and methods

[redacted]

5.3 Results and discussion

[redacted]

5.4 Conclusion

Iodine itself, particularly as vapour, and in solutions is reported as strong eye irritant. Iodine is currently not classified as an eye irritant according to Directive 67/548/EEC.

Section A6.1.4.1/01-04 Acute Eye Irritation

Annex Point IIA VI.6.1.4

5.4.1 Reliability [redacted]

5.4.2 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]

Section A6.1.4.2/01-04 Acute Skin Irritation

Annex Point IIA VI.6.1.4

[redacted]

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		1	**REFERENCE**
1.1	**Reference**	[1]	Hazardous Substance Data Bank (HSDB), p. 5 Doc. No. 591-004 (published); Section A.6.1.4.2/01
		[2]	INCHEM: Poison Information Monograph on Iodine (PIM 280), p. 8 (p. 51 of the whole document 591-008) http://www.inchem.org/documents/pims/pharm/iodine.htm Doc. No. 591-008 (published); Section A.6.1.4.2/02
		[3]	GESTIS-database on hazardous substances of the German institutions for statutory accident insurance and prevention ("Berufsgenossenschaften"), p. 2 www.hvbg.de/bgia/gestis-database Doc. No. 592-050 (published); Section A.6.1.4.2/03
		[4]	ESIS: European chemical Substances Information System Doc. No. 991-003 (published); Section A.6.1.4.2/04
1.2	**Data protection**	[redacted]	
1.2.1	Data owner	[redacted]	
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**	Not applicable [redacted]	
2.2	**GLP**	Not applicable [redacted]	
2.3	**Deviations**	Not applicable [redacted]	
		3	**MATERIALS AND METHODS**
3.1	**Test material**	Iodine	
3.2	**Test method**	Not applicable [redacted]	

Section A6.1.4.2/01-04 Acute Skin Irritation

Annex Point IIA VI.6.1.4

4 RESULTS AND DISCUSSION

4.1 Results

[redacted]

4.2 Discussion

[redacted]

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

[redacted]

5.2 Results and discussion

[redacted]

Section A6.1.4.2/01-04 Acute Skin Irritation

Annex Point IIA VI.6.1.4

5.3	**Conclusion**	Iodine, in particular in alcoholic solutions, is reported as a skin irritant but it is currently not classified with regard to skin irritation according to Directive 67/548/EEC.
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]

Section A6.1.4.2/05 Acute Skin Irritation

Annex Point IIA VI.6.1.4

[redacted]

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1 REFERENCE

1.1	**Reference**	[5]	Lee, S. K. et al (2005): Allergic contact dermatitis from Iodine preparations: a conundrum; Department of Dermatology, University of California, School of Medicine, USA; Contact Dermatitis 2005: 2005, Vol. 52, n°4, pp. 184-187, Study No.: not indicated; Doc. No. 592-046 (publication), Section A6.1.4.2/05
1.2	**Data protection**	[redacted]	
1.2.1	Data owner	[redacted]	
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**	Not applicable [redacted]

3 MATERIALS AND METHODS

3.1	**Test material**	Iodine
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 subjects**	
3.2.1	Species	Human
3.2.2	Strain	Caucasian (23/24); Hispanic (1/24)
3.2.3	Source	Volunteers
3.2.4	Sex	Both sexes (6 men, 18 women)
3.2.5	Age/weight at study initiation	[redacted]
3.2.6	Number of humans per group	[redacted]
3.2.7	Control subjects	[redacted]

Section A6.1.4.2/05 Acute Skin Irritation

Annex Point IIA VI.6.1.4

3.3	**Administration/ Exposure**	Dermal
3.3.1	Application	
3.3.1.1	Preparation of test substance	[redacted]
3.3.1.2	Test site and preparation of test site	[redacted]
3.3.2	Occlusion	[redacted]
3.3.3	Vehicle	[redacted]
3.3.4	Concentration in vehicle	[redacted]
3.3.5	Total volume applied	[redacted]
3.3.6	Removal of test substance	[redacted]
3.3.7	Duration of exposure	[redacted]
3.3.8	Post-exposure period	[redacted]
3.3.9	Controls	[redacted]
3.4	**Examinations**	
3.4.1	Clinical signs	[redacted]
3.4.2	Dermal examination	[redacted]
3.4.2.1	Scoring system	[redacted]
3.4.2.2	Examination time points	[redacted]
3.4.3	Other examinations	[redacted]
3.5	**Further remarks**	[redacted]

4 RESULTS AND DISCUSSION

4.1	**Average score**	
4.1.1	Erythema	[redacted]
4.1.2	Oedema	[redacted]
4.2	**Reversibility**	[redacted]
4.3	**Other**	[redacted]

Section A6.1.4.2/05 Acute Skin Irritation

Annex Point IIA VI.6.1.4

4.4 Overall result

[redacted]

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

[redacted]

5.2 Results and discussion

[redacted]

Section A6.1.4.2/05 Acute Skin Irritation

Annex Point IIA VI.6.1.4

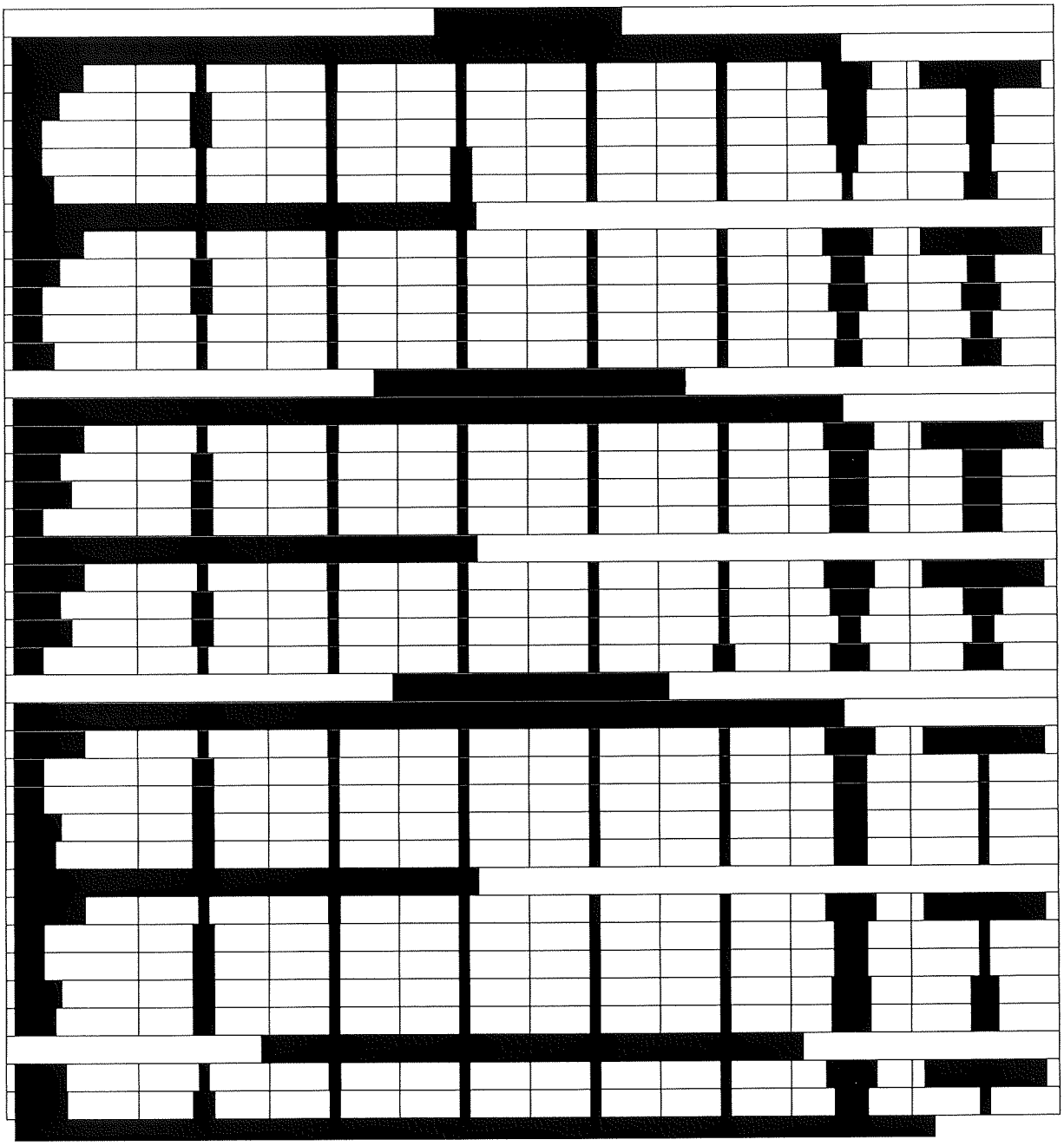
5.3	**Conclusion**	Iodine (0.5%-1%) [redacted] is a skin irritant if tested under stringent test conditions (occlusive skin contact for 24 hours). [redacted] iodine (10%) is almost non-irritant. Although Iodine and primarily Iodine [redacted] are reported as irritant to skin, Iodine is currently not classified with regard to skin irritation according to Directive 67/548/EEC (risk phrase R38: Irritating to skin). When [redacted] Iodine is applied to skin, the formation of free iodic acid [redacted] classified as corrosive) is likely, due to the water content of the skin (surface). Free iodic acid could be considered to be responsible for the irritation properties of Iodine. This and the findings that 5%-10% Iodine [redacted] caused erythema do not justify a irritation toxicity study (dermal) with [redacted] Iodine because of animal welfare reasons. [redacted]
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]

Table A6.1.4.2./05-1 Results of skin irritation study



Section A6.1.5/01 Skin sensitisation

Annex Point IIA VI.6.1.5

Guinea pig maximisation test (GPMT)

			Official use only
		1 REFERENCE	
1.1	**Reference**	[redacted]	
1.2	**Data protection**	[redacted]	
1.2.1	Data owner	[redacted]	
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] Directive 96/54/EC, B.6	
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	Preparation of test substance for application	[redacted]	
3.1.2.5	Pre-test performed on irritant effects	[redacted]	
3.2	**Test Animals**		
3.2.1	Species	Guinea pigs	
3.2.2	Strain	Albino Dunkin Hartley	
3.2.3	Source	[redacted]	
3.2.4	Sex	male	
3.2.5	Age/weight at study initiation	[redacted]	

Section A6.1.5/01 Skin sensitisation

Guinea pig maximisation test (GPMT)

Annex Point IIA VI.6.1.5

3.2.6	Number of animals per group	[redacted]
3.2.7	Control animals	[redacted]
3.3	**Administration/ Exposure**	State study type: Adjuvant
3.3.1	Induction schedule	[redacted]
3.3.2	Way of Induction	Intradermal and topical Occlusive dressing
3.3.3	Concentrations used for induction	[redacted]
3.3.4	Concentration Freund's Complete Adjuvant (FCA)	[redacted]
3.3.5	Challenge schedule	[redacted]
3.3.6	Concentrations used for challenge	[redacted]
3.3.7	Rechallenge	[redacted]
3.3.8	Scoring schedule	[redacted]
3.3.9	Removal of the test substance	[redacted]
3.3.10	Positive control substance	[redacted]
3.3.11	Negative control	[redacted]
3.4	**Examinations**	
3.4.1	Pilot study	[redacted]

Section A6.1.5/01 Skin sensitisation
Annex Point IIA VI.6.1.5 Guinea pig maximisation test (GPMT)

3.5 Further remarks [redacted]

4 RESULTS AND DISCUSSION

4.1 Results of pilot studies [redacted]

4.2 Results of test

4.2.1 24h after challenge [redacted]

4.2.2 48h after challenge [redacted]

Section A6.1.5/01 Skin sensitisation

Annex Point IIA VI.6.1.5 Guinea pig maximisation test (GPMT)

4.2.3 Other findings

[redacted]

4.3 Overall result

[redacted]

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

[redacted]

5.2 Results and discussion

[redacted]

Section A6.1.5/01 Skin sensitisation

Annex Point IIA VI.6.1.5

Guinea pig maximisation test (GPMT)

5.3 Conclusion

The test material did not meet the criteria for classification as a sensitiser according to EU labelling regulations Commission Directive 93/21/EEC. No symbol and risk phrase are required, the test substance is classified as non-sensitiser.

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]

Section A6.1.5/01 Skin sensitisation

Annex Point IIA VI.6.1.5

Guinea pig maximisation test (GPMT)

Table A6.1.5/01-1 Detailed information including induction/challenge/scoring schedule for skin sensitisation test

	GPMT		Observations*1) *2)/Remarks
	Day of treatment	Application	
[redacted]			

Table A6.1.5/01-2 Result of skin sensitisation test

[redacted]			

Section A6.2/01-09 Metabolism studies in mammals. Basic toxicokinetics including dermal absorption

Annex Point IIA VI.6.2

[redacted]

Official use only

1 REFERENCE

1.1 Reference

[1] EUROPEAN COMMISSION, HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL, SCF, Scientific Committee on Food: Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Iodine (expressed on 26 September 2002).
http://europa.eu.int/comm/food/fs/sc/scf/out146_en.pdf
Doc. No. 592-031 (published); Section A6.2/01

[2] INCHEM: Summary of Evaluations Performed by the Joint FAO/WHO Expert Committee on Food Additives: Iodine
http://www.inchem.org/documents/jecfa/jecmono/v024je11.htm
Doc. No. 591-008 (published); Section A6.2/02

[3] INCHEM: Poison Information Monograph on Iodine (PIM 280)
http://www.inchem.org/documents/pims/pharm/iodine.htm
Doc. No. 591-008 (published); Section A6.2/03

[4] GESTIS-database on hazardous substances of the German institutions for statutory accident insurance and prevention ("Berufsgenossenschaften")
www.hvbg.de/bgia/gestis-database
Doc. No. 592-050 (published); Section A6.2/04

[5] Forth, W.; Henschler D., Rummel W.: Schilddrüsenhormone und Thyreostatika; Allgemeine und spezielle Pharmakologie und Toxikologie; 4th edition; ISBN 3-437-42521-8
Doc. No. 592-052 (published); Section A6.2/05

[6] TOXICOLOGICAL PROFILE FOR IODINE (April 2004); U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, Public Health Service, Agency for Toxic Substances and Disease Registry
http://www.atsdr.cdc.gov/toxprofiles/tp158.pdf
Doc. No. 581-009 (published); Section A6.2/06

[7] Toxikologisch-arbeitsmedizinische Begründung von MAK-Werten; DFG Evaluation for MAK Values; The MAK-Collection for Occupational Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area; ISBN 3-527-19030-9
Doc. No. 592-051 *(published)*; Section A6.2/07

[8] US Food and Nutrition Board (2001). Dietary Reference Intakes. A report of the Institute of Medicine. National Academy Press, Washington, DC.
Doc. No. 692-032 (published); Section A6.2/08

[9] Köhl, W., Kirbach. I. (2006): Expert Evaluation provided for Dossier Preparation in Accordance with Directive 98/8/EC: ADME of Iodine; SCC Scientific Consulting GmbH
Doc. No. 519-002 (unpublished); Section A6.2/09

1.2 Data protection [redacted]

1.2.1 Data owner [redacted]

Section A6.2/01-09 Metabolism studies in mammals. Basic toxicokinetics including dermal absorption

Annex Point IIA VI.6.2

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 Not applicable.

[redacted]

2.2 GLP [redacted]

2.3 Deviations Not applicable [redacted]

3 MATERIALS AND METHODS

3.1 Test material and methods [redacted]

4 RESULTS AND DISCUSSION

4.1 General results

Iodine is an essential dietary element for mammals being required for the synthesis of the thyroid hormones which control metabolisms, e.g. of fat, carbohydrate and protein, and increase the metabolic rate of almost all cells in the body. Iodine through its role in thyroid hormones is of vital importance for human health and plays an important role in normal growth and development.

There is a lot of data derived from experience in humans with dietary supplements and pharmaceuticals, but only a limited number of animal studies are available. Therefore, not a single study but a comprehensive description of ADME is provided.

4.1.1 Absorption [redacted]

[redacted]

4.1.2 Distribution

[redacted]

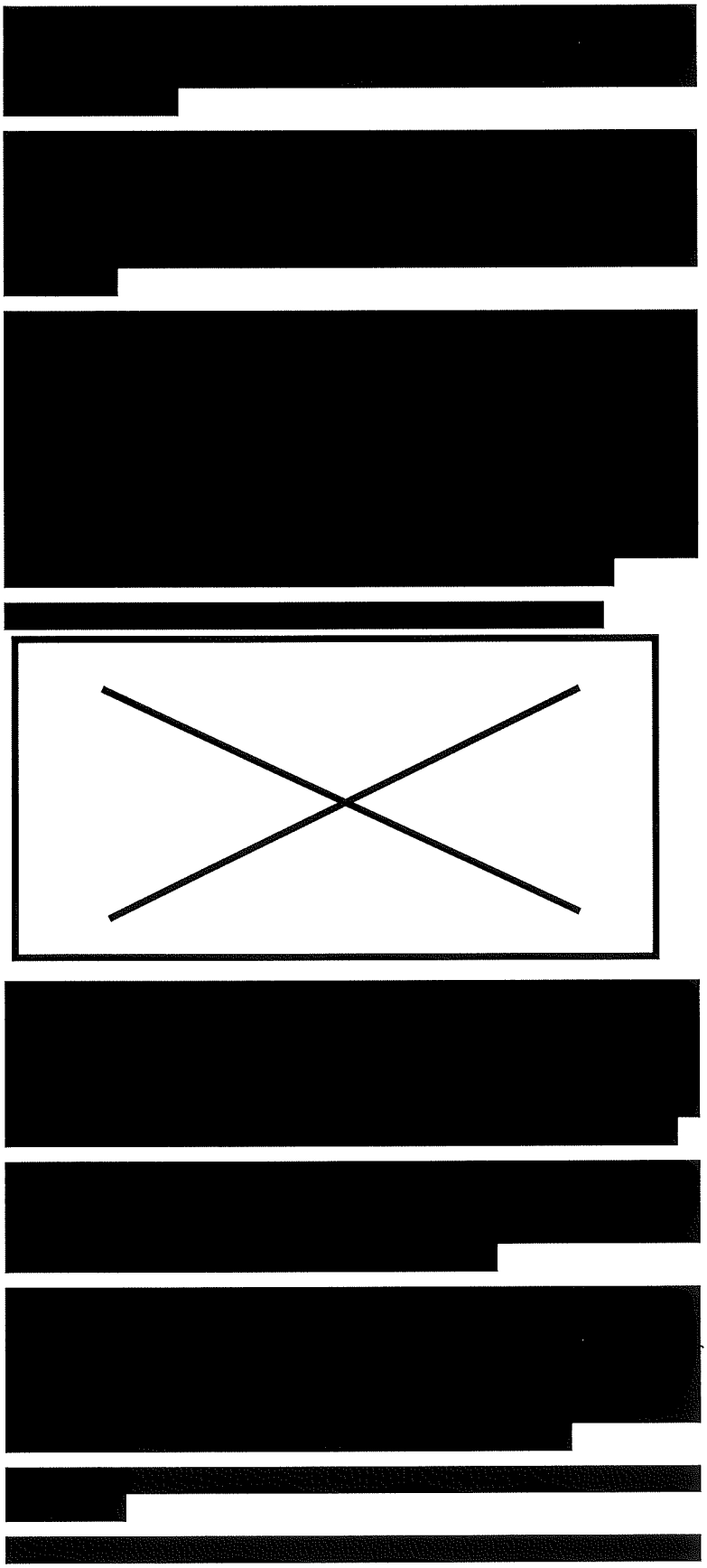
Section A6.2/01-09
Annex Point IIA VI.6.2

Metabolism studies in mammals. Basic toxicokinetics including dermal absorption

Section A6.2/01-09
Annex Point IIA VI.6.2

Metabolism studies in mammals. Basic toxicokinetics including dermal absorption

4.1.3 Metabolism



Section A6.2/01-09
Annex Point IIA VI.6.2

Metabolism studies in mammals. Basic toxicokinetics including dermal absorption

[redacted]

4.1.4 Excretion

[redacted]

4.1.5 Interferences

[redacted]

[redacted]

4.2 Percutaneous absorption

[redacted]

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

[redacted]

5.2 Results and discussion

[redacted]

Section A6.2/01-09 Metabolism studies in mammals. Basic toxicokinetics including dermal absorption

Annex Point IIA VI.6.2

[redacted]

5.3 Conclusion

The complex of ADME of Iodine in mammals, in particular in humans is well-known because Iodine is an essential dietary element and very important to health, normal growth and development. The available data in humans allow a scientifically valid evaluation of ADME of Iodine.

Animal data are of limited value because of species differences in basal metabolic rate and in Iodine metabolism. Thus, the performance of a further animal study is scientifically not reasonable.

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]

Section A6.2/01-09

Annex Point IIA VI.6.2

Metabolism studies in mammals. Basic toxicokinetics including dermal absorption

Remarks	[redacted]

Section A6.2 Annex Point IIA6.2	Percutaneous absorption and Toxicokinetics of Iodine	
	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]	
	Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	[redacted]	
Evaluation of applicant's justification	[redacted]	
Conclusion	[redacted]	
Remarks	[redacted]	

Section A6.3.1/01-04 Repeated dose toxicity

Annex Point IIIA, VI.6.3 Low dose oral Iodide supplementation in humans

[redacted]

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1 REFERENCE

1.1 Reference

[1] Gardner D.F., Centor RM, Utiger R.D. (1988): Effects of low dose oral supplementation on thyroid function in normal men. Clin. Endocrinol. 28: 283-288.

Doc. No. 692-036 (published); Section A6.3.1/01

Further references for LO(A)EL/NO(A)EL derivation:

[2] FNB (2001): Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium and Zink. Food and Nutrition Board (FNB)/Institute of Medicine (IOM). National Academy Press, Washington, DC, USA. p. 281

Doc. No. 692-032 (published); Section A6.3.1/02

[3] EUROPEAN COMMISSION, HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL, SCF, Scientific Committee on Food: Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Iodine (expressed on 26 September 2002). http://europa.eu.int/comm/food/fs/sc/scf/out146_en.pdf

Doc. No. 592-031 (published); Section A6.3.1/03

[4] Federal Institute for Risk assessment (BfR, 2006): Use of Minerals in Food; Toxicological and nutritional-physiological aspects; Part II; p. 198
ISBN 3-938163-11-9
http://www.bfr.bund.de/cm/238/use_of_minerals_in_foods.pdf

Doc. No. 592-080 (published); Section A6.3.1/04

1.2 Data protection [redacted]

1.2.1 Data owner [redacted]

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 Not applicable, [redacted]

2.2 GLP Not applicable, [redacted]

2.3 Deviations Not applicable, [redacted]

Section A6.3.1/01-04 Repeated dose toxicity

Annex Point IIIA, VI.6.3 Low dose oral Iodide supplementation in humans

3 MATERIALS AND METHODS

3.1	**Test material**	Sodium iodide (CAS No. 7681-82-5)
3.2	**Test Persons**	
3.2.1	Species	Human
3.2.2	Sex	Male
3.2.3	Age/weight at study initiation	[redacted]
3.2.4	Number of test persons per group	[redacted]
3.2.5	Control test persons and baseline values	[redacted]
3.3	**Administration/ Exposure**	Oral (after an initial i.v. bolus of 500 µg TRH)
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]
3.4	**Examinations**	
3.4.1	Observations	[redacted]

Section A6.3.1/01-04 Repeated dose toxicity

Annex Point IIIA, VI.6.3 Low dose oral Iodide supplementation in humans

3.4.1.1 Clinical signs

3.4.1.2 Mortality

3.4.2 Body weight

3.4.3 Food consumption

3.4.4 Water consumption

3.4.5 Ophthalmoscopic examination

3.4.6 Haematology

3.4.7 Clinical Chemistry

3.4.8 Urinalysis

3.4.9 Statistics

3.5 Sacrifice and pathology

3.6 Further remarks

4 RESULTS AND DISCUSSION

4.1 Observations

4.1.1 Clinical signs

4.2 Body weight gain

4.3 Blood analysis

4.3.1 Clinical chemistry

Section A6.3.1/01-04 Repeated dose toxicity

Annex Point IIIA, VI.6.3 Low dose oral Iodide supplementation in humans

[redacted]

4.3.2 Urinalysis

[redacted]

4.4 Other

[redacted]

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

[redacted]

5.2 Results and discussion

[redacted]

5.3 Conclusion

Thus, low Iodide supplementation of 1500-4500 µg/day, additional to a basic Iodide consumption of about 700-800 µg Iodide/day (as estimated for the USA) has a significant inhibitory effect on the thyroid secretion in healthy men.

5.3.1 LOEL

If a basic Iodide consumption of about 800 µg Iodide/day (as estimated for the USA) is considered:

2300 µg/day

[redacted]

If a basic Iodide consumption of about 300 µg Iodide/day, derived from the Iodide excretion is considered:

1800 µg/day

[redacted]

5.3.2 Upper Intake Level (USA)

1200 µg/day [redacted]

Section A6.3.1/01-04 Repeated dose toxicity

Annex Point IIIA, VI.6.3 Low dose oral Iodide supplementation in humans

5.3.3	Upper Intake Level (Europe)	600 µg/day [redacted]
5.3.4	Other	[redacted]
5.3.5	Reliability	[redacted]
5.3.6	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]

Section A6.3.1/01-04 Repeated dose toxicity

Annex Point IIA6.3.1

Low dose oral Iodide supplementation in humans

Table A6.3.1/01-04-1: Results of urinalysis and clinical chemistry: Urinary Iodide excretion and serum Iodide concentrations before and after administration

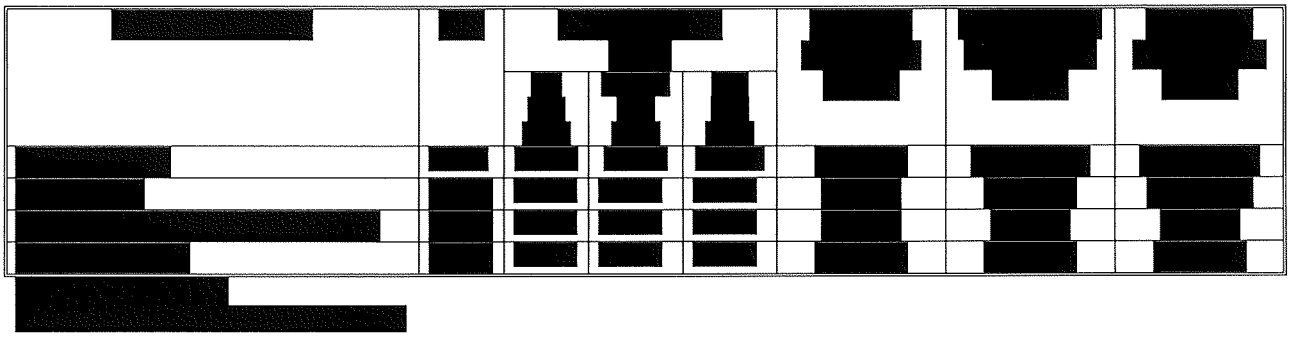


Table A6.3.1/01-04-2: Results of clinical chemistry: Serum thyroid hormone concentrations before and after administration

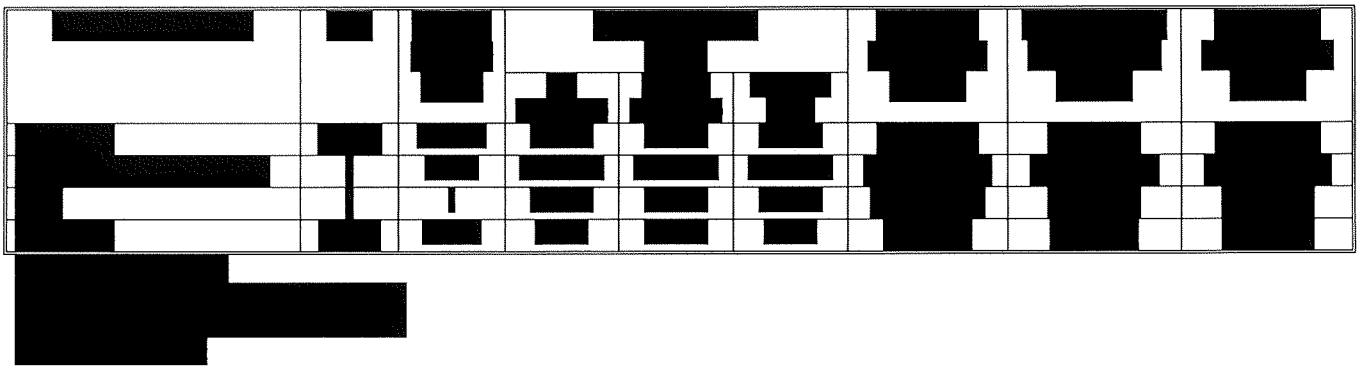
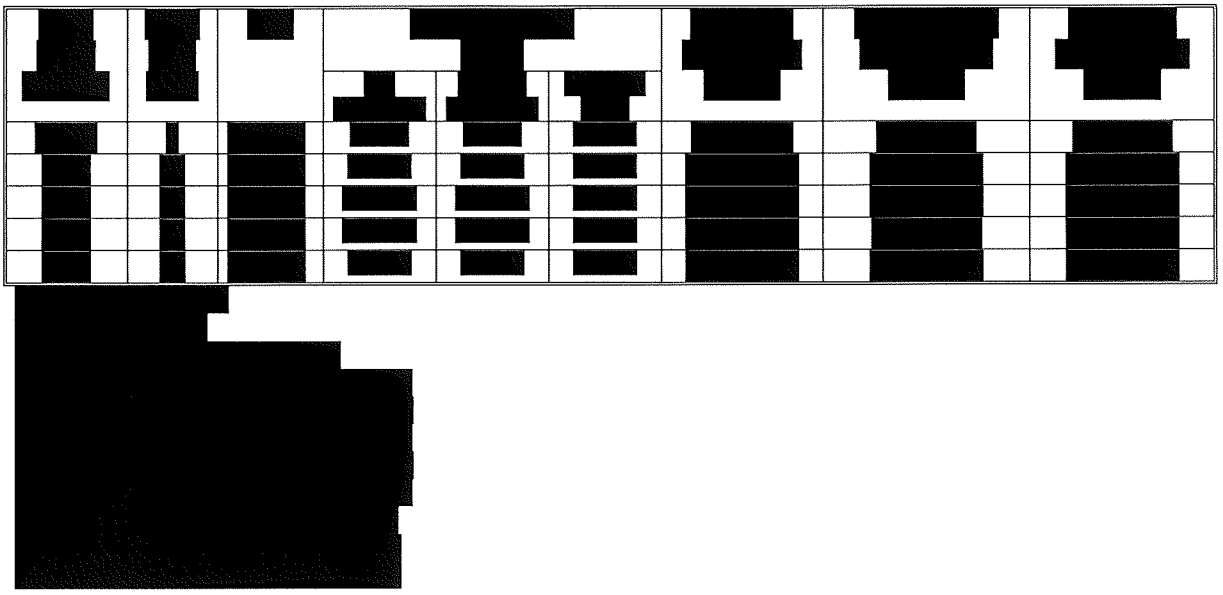


Table A6.3.1/01-04-3: Results of clinical chemistry: Effect of Iodide on basal and TRH-stimulated serum TSH concentration



Section A6.3.1/05 Repeated dose toxicity

Annex Point IIA, VI.6.3 Low dose oral Iodide supplementation in humans

[redacted]

Official use only

1 REFERENCE

1.1 Reference

[1] Paul T., Meyers B., Witorsch R.J., Pino S., Chipkin S., Ingbar S.H., Braverman L.E. (1988): The effect of small increases in dietary iodine on thyroid function in euthyroid subjects. Metabolism 37: 121-124.

Doc. No. 692-037 (published); Section A6.3.1/05

Further references for LO(A)EL/NO(A)EL derivation:

[2] FNB (2001): Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium and Zink. Food and Nutrition Board (FNB)/Institute of Medicine (IOM). National Academy Press, Washington, DC, USA. p. 281

Doc. No. 692-032 (published); Section A6.3.1/02

[3] EUROPEAN COMMISSION, HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL, SCF, Scientific Committee on Food: Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Iodine (expressed on 26 September 2002). http://europa.eu.int/comm/food/fs/sc/scf/out146_en.pdf

Doc. No. 592-031 (published); Section A6.3.1/03

[4] Federal Institute for Risk assessment (BfR, 2006): Use of Minerals in Food; Toxicological and nutritional-physiological aspects; Part II; p. 198
ISBN 3-938163-11-9
http://www.bfr.bund.de/cm/238/use_of_minerals_in_foods.pdf

Doc. No. 592-080 (published); Section A6.3.1/04

1.2 Data protection [redacted]

1.2.1 Data owner [redacted]

1.2.2 Companies with letter of access [redacted]

1.2.3 Criteria for data protection [redacted]

Section A6.3.1/05 Repeated dose toxicity

Annex Point IIA, VI.6.3 Low dose oral Iodide supplementation in humans

2 GUIDELINES AND QUALITY ASSURANCE

2.1 Guideline study Not applicable, [redacted]

2.2 GLP Not applicable, [redacted]

2.3 Deviations Not applicable, [redacted]

3 MATERIALS AND METHODS

3.1 Test material Sodium iodide (CAS No. 7681-82-5)

3.2 Test Persons

3.2.1 Species Human

3.2.2 Sex Male and female

3.2.3 Age/weight at study initiation [redacted]

3.2.4 Number of test persons per group [redacted]

3.2.5 Control test persons and baseline values [redacted]

3.3 Administration/ Exposure Oral (after an initial i.v. bolus of 500 µg TRH)

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]

Section A6.3.1/05 Repeated dose toxicity

Annex Point IIA, VI.6.3 Low dose oral Iodide supplementation in humans

3.3.4.4 Concentration in vehicle

3.3.4.5 Total volume applied

3.3.4.6 Controls

3.4 Examinations

3.4.1 Observations

3.4.1.1 Clinical signs

3.4.1.2 Mortality

3.4.2 Body weight

3.4.3 Food consumption

3.4.4 Water consumption

3.4.5 Ophthalmoscopic examination

3.4.6 Haematology

3.4.7 Clinical Chemistry

3.4.8 Urinalysis

3.4.9 Statistics

3.5 Sacrifice and pathology

3.6 Further remarks

4 RESULTS AND DISCUSSION

4.1 Observations

4.1.1 Clinical signs

4.2 Body weight gain

4.3 Blood analysis

Section A6.3.1/05 Repeated dose toxicity

Annex Point IIA, VI.6.3 Low dose oral Iodide supplementation in humans

4.3.1 Clinical chemistry

[redacted]

4.3.2 Urinalysis

[redacted]

4.4 Other

[redacted]

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

[redacted]

5.2 Results and

[redacted]

Section A6.3.1/05 Repeated dose toxicity

Annex Point IIA, VI.6.3 Low dose oral Iodide supplementation in humans

discussion

[redacted]

5.3 Conclusion

An increase in dietary Iodine of 1,500 µg daily can induce subtle changes in the pituitary-thyroid function, probably by inhibiting thyroid hormone release. Smaller Iodine supplements of 250 and 500 µg daily did not affect the thyroid function.

5.3.1 LOEL

[redacted]

1700 µg/day

[redacted]

5.3.2 Upper Intake Level (USA)

1100 µg/day [redacted]

5.3.3 Upper Intake Level (Europe)

The LOEL of 1700 µg/day [redacted]

[redacted]

LO(A)EL of 1800 µg/day [redacted] and a NOEL of 600 µg/day -

The LOEL of 1800 µg/day is supported by the present study [redacted]

5.3.4 Other [redacted]

5.3.5 Reliability [redacted]

5.3.6 Deficiencies [redacted]

Evaluation by Competent Authorities

EVALUATION BY RAPPORTEUR MEMBER STATE

Section A6.3.1/05 Repeated dose toxicity

Annex Point IIA, VI.6.3 Low dose oral Iodide supplementation in humans

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

Section A6.3.1/05 **Repeated dose toxicity**

Annex Point IIA6.3.1 Low dose oral Iodide supplementation in humans

Table A6.3.1/05-1: Results of urinalysis and clinical chemistry: Urinary Iodine excretion and serum Iodide concentrations before and after administration in men and women

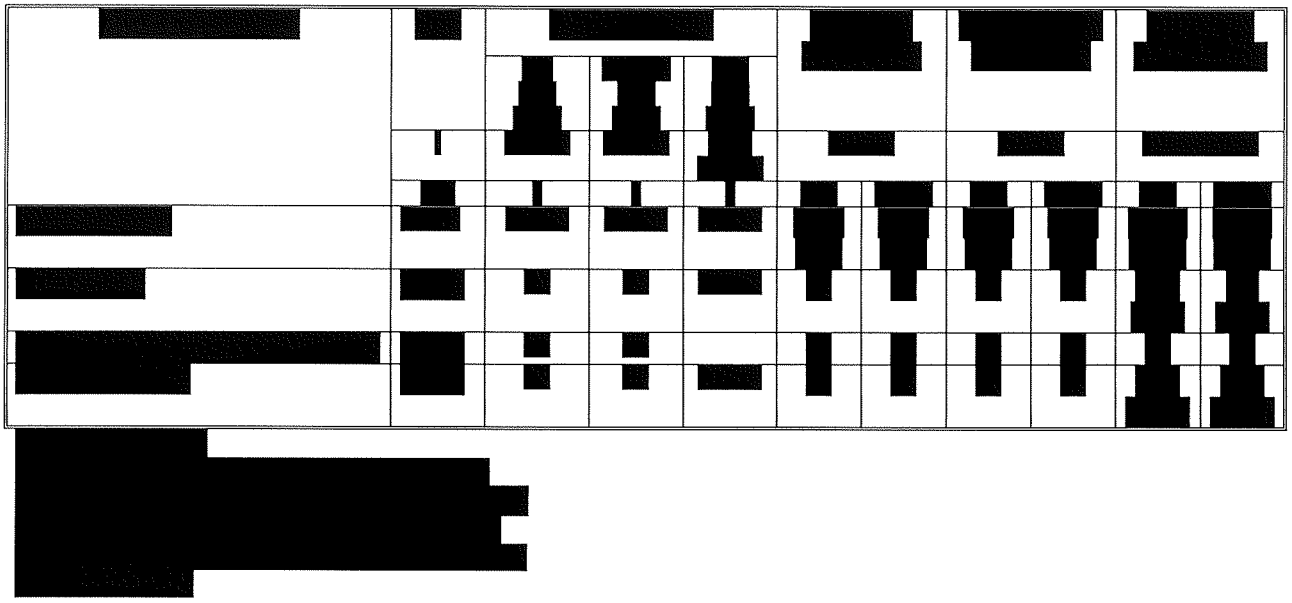
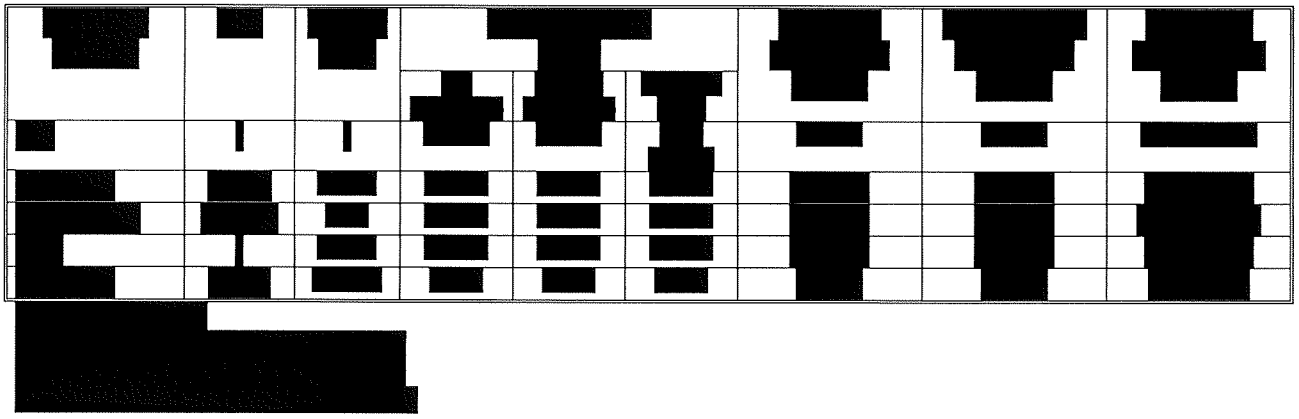


Table A6.3.1/05-2: Results of clinical chemistry: Serum thyroid hormone concentrations before and after administration



ection A6.3.1/06 **Repeated dose toxicity**

Annex Point IIA, VI.6.3 **Oral toxicity test in rat**

Section A6.3.2
Annex Point IIA, VI.6.3

Repeated/subacute toxicity
Dermal

JUSTIFICATION FOR NON-SUBMISSION OF DATA		Official use only
Other existing data [X]	Technically not feasible [ ] Scientifically unjustified [ ]	
Limited exposure [ ]	Other justification [X]	
Detailed justification:	[redacted]	

Evaluation by Competent Authorities

EVALUATION BY RAPPORTEUR MEMBER STATE

Date	[redacted]
Evaluation of applicant's justification	[redacted]
Conclusion	[redacted]
Remarks	

Section A6.3.3 Repeated dose toxicity

Annex Point IIA VI.6.3. **Inhalation**

	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [X]	Technically not feasible [ ] Scientifically unjustified [ ]	
Limited exposure [ ]	Other justification [X]	
Detailed justification:	[redacted]	

	Evaluation by Competent Authorities
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	[redacted]
Evaluation of applicant's justification	[redacted]
Conclusion	[redacted]
Remarks	

Section A6.4.1/01
Annex Point IIA VI.6.4

Subchronic oral toxicity test
(including repeated oral toxicity test only for T_3 and T_4)
Rat

			Official use only
		1 REFERENCE	
1.1	**Reference**	Sherer, T.T., Thrall, K.D., Bull, R.J. (1991): Comparison by Iodine and Iodide in male and female Rats; J Toxicol. Environ. Health, 32, pp 89-101; Doc. No. 592-027, Section A.6.4.1/01	X1
1.2	**Data protection**	[redacted]	
1.2.1	Data owner	[redacted]	
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] OECD guideline 408 is of 1998, [redacted]	
2.2	**GLP**	[redacted]	
2.3	**Deviations**	Not applicable [redacted] Deviations if compared with OECD 408: - purity of the test material is not specified - 12 animals/group instead of at 20 animals/group - no information on clinical observations and ophthalmological examinations - no information on food and water consumption and initial body weight	
		3 MATERIALS AND METHODS	
3.1	**Test material**	(1) Iodine (2) Iodide (from Sodium iodide)	
3.1.1	Lot/Batch number	[redacted]	
3.1.2	Specification	[redacted]	
3.1.3	Description	[redacted]	
3.1.4	Purity	[redacted]	
3.1.5	Stability	[redacted]	
3.2	**Test Animals**		
3.2.1	Species	Rat	
3.2.2	Strain	Sprague-Dawley	
3.2.3	Source	[redacted]	
3.2.4	Sex	Male, female	
3.2.5	Age/weight at study initiation	[redacted]	

Section A6.4.1/01 **Subchronic oral toxicity test**
(including repeated oral toxicity test only for T_3 and T_4)

Annex Point IIA VI.6.4 **Rat**

3.2.6	Number of animals per group	
3.2.7	Control animals	
3.3	**Administration/ Exposure**	Oral (via drinking water)
3.3.1	Duration of treatment	
3.3.2	Frequency of exposure	
3.3.3	Postexposure period	
3.3.4	Type	
3.3.5	Concentration	X2
3.3.6	Vehicle	
3.3.7	Concentration in vehicle	
3.3.8	Total volume applied	
3.3.9	Controls	
3.4	**Examinations**	
3.4.1	Observations	
3.4.1.1	Clinical signs	
3.4.1.2	Mortality	
3.4.2	Body weight	
3.4.3	Food consumption	
3.4.4	Water consumption	
3.4.5	Ophthalmoscopic examination	
3.4.6	Haematology	

Section A6.4.1/01 **Subchronic oral toxicity test**
(including repeated oral toxicity test only for T_3 and T_4)

Annex Point IIA VI.6.4 **Rat**

3.4.7	Clinical Chemistry	[redacted]
3.4.8	Urinalysis	[redacted]
3.5	**Sacrifice and pathology**	
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	**Water Consumption**	[redacted]
4.5	**Ophthalmoscopic examination**	[redacted]
4.6	**Blood analysis**	
4.6.1	Haematology	[redacted]

Section A6.4.1/01 **Subchronic oral toxicity test**
(including repeated oral toxicity test only for T_3 and T_4)

Annex Point IIA VI.6.4 **Rat**

4.6.2 Clinical chemistry

4.6.3 Urinalysis

4.7 Sacrifice and pathology

4.7.1 Organ weights

4.7.2 Gross and histopathology

4.8 Other

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and

Section A6.4.1/01 **Subchronic oral toxicity test**
(including repeated oral toxicity test only for T_3 and T_4)
Annex Point IIA VI.6.4 **Rat**

methods

[redacted]

5.2 Results and discussion

[redacted]

Section A6.4.1/01 **Subchronic oral toxicity test**
(including repeated oral toxicity test only for T_3 and T_4)
Annex Point IIA VI.6.4 **Rat**

5.3 Conclusion

5.3.1 LO(A)EL *target: plasma thyroid hormone levels*

Iodine:
1.4 mg/kg bw/day (target: plasma thyroid hormone levels)

[redacted]

The LO(A)EL for repeated intake is 14 mg/kg bw/day (target: plasma thyroid hormone levels [redacted]

Iodide:
0.14 mg/kg bw/day (target: plasma thyroid hormone levels)

The LO(A)EL for subchronic [redacted] in female rats at 1 mg/L after 100 days of treatment.

The LO(A)EL for repeated intake is also 0.14 mg/kg bw/day (target: plasma thyroid hormone levels [redacted]

LO(A)EL *target: thyroid enlargement*

Iodine:
> 14 mg/kg bw/day (target: thyroid enlargement)

Iodide:
1.4 mg/kg bw/day (target: thyroid enlargement)

[redacted]

5.3.2 NO(A)EL *target: plasma thyroid hormone levels*

Iodine:
0.42 mg/kg bw/day (target: plasma thyroid hormone levels)

[redacted]

The NO(A)EL for repeated intake is 1.4 mg/kg bw/day (target: plasma thyroid hormone levels), [redacted]

Iodide:
<0.14 mg/kg bw/day (target: plasma thyroid hormone levels)

[redacted]

The NO(A)EL for repeated intake is also <0.14 mg/kg bw/day (target: plasma thyroid hormone levels), [redacted]

NO(A)EL *target: thyroid enlargement*

Iodine:
14 mg/kg bw/day (target: thyroid enlargement)

Iodide:
0.42 mg/kg bw/day (target: thyroid enlargement)

[redacted]

Section A6.4.1/01 **Subchronic oral toxicity test**
(including repeated oral toxicity test only for T_3 and T_4)

Annex Point IIA VI.6.4 **Rat**

[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]

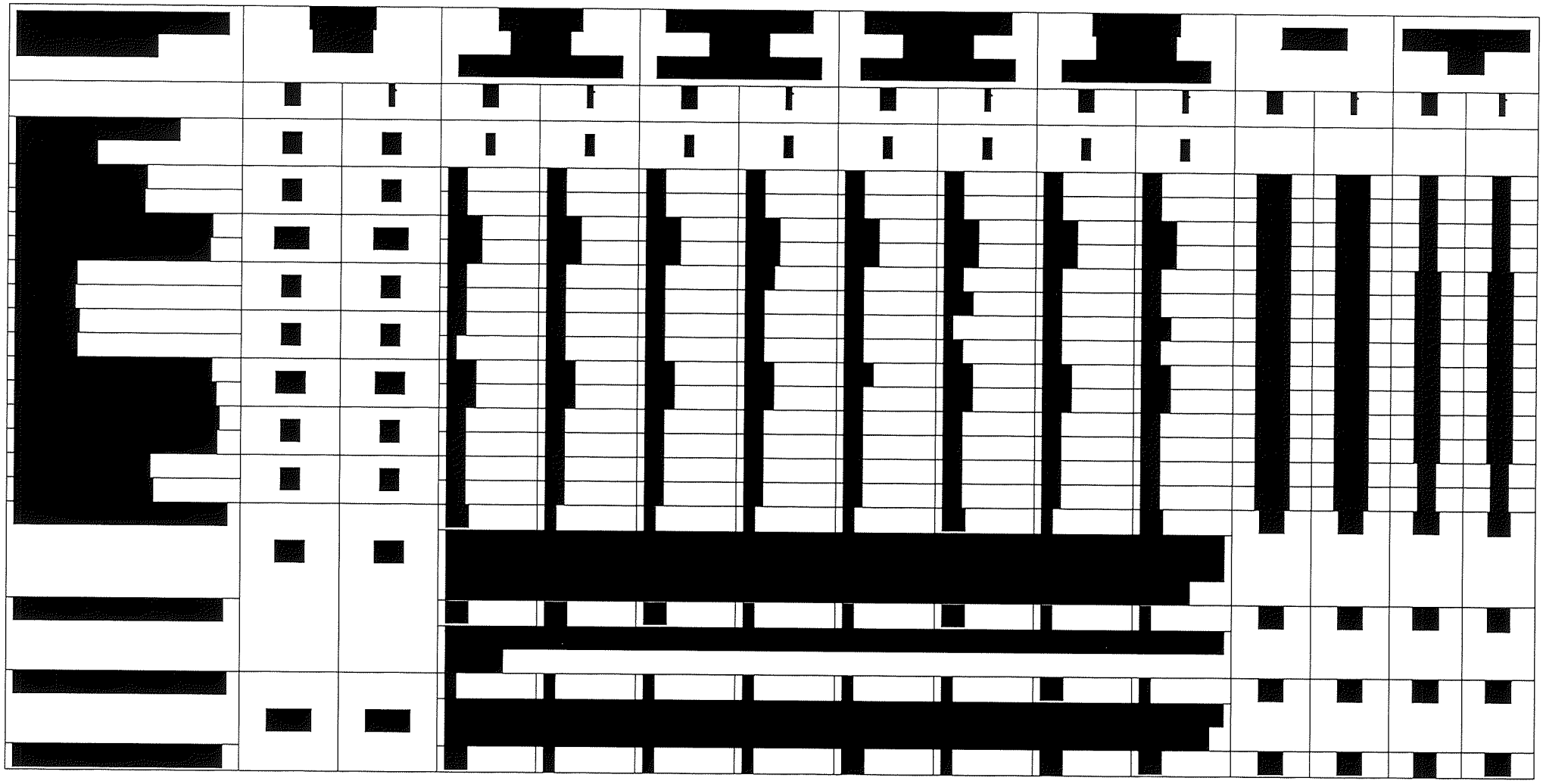
Conclusion [redacted]

Reliability [redacted]

Acceptability [redacted]

Remarks [redacted]

Table A6.4.1/01-1: Results of haematology and clinical chemistry in rat subjected to varying concentration of Iodine (I_2) or Iodide (I^-) on their drinking water of 100 days



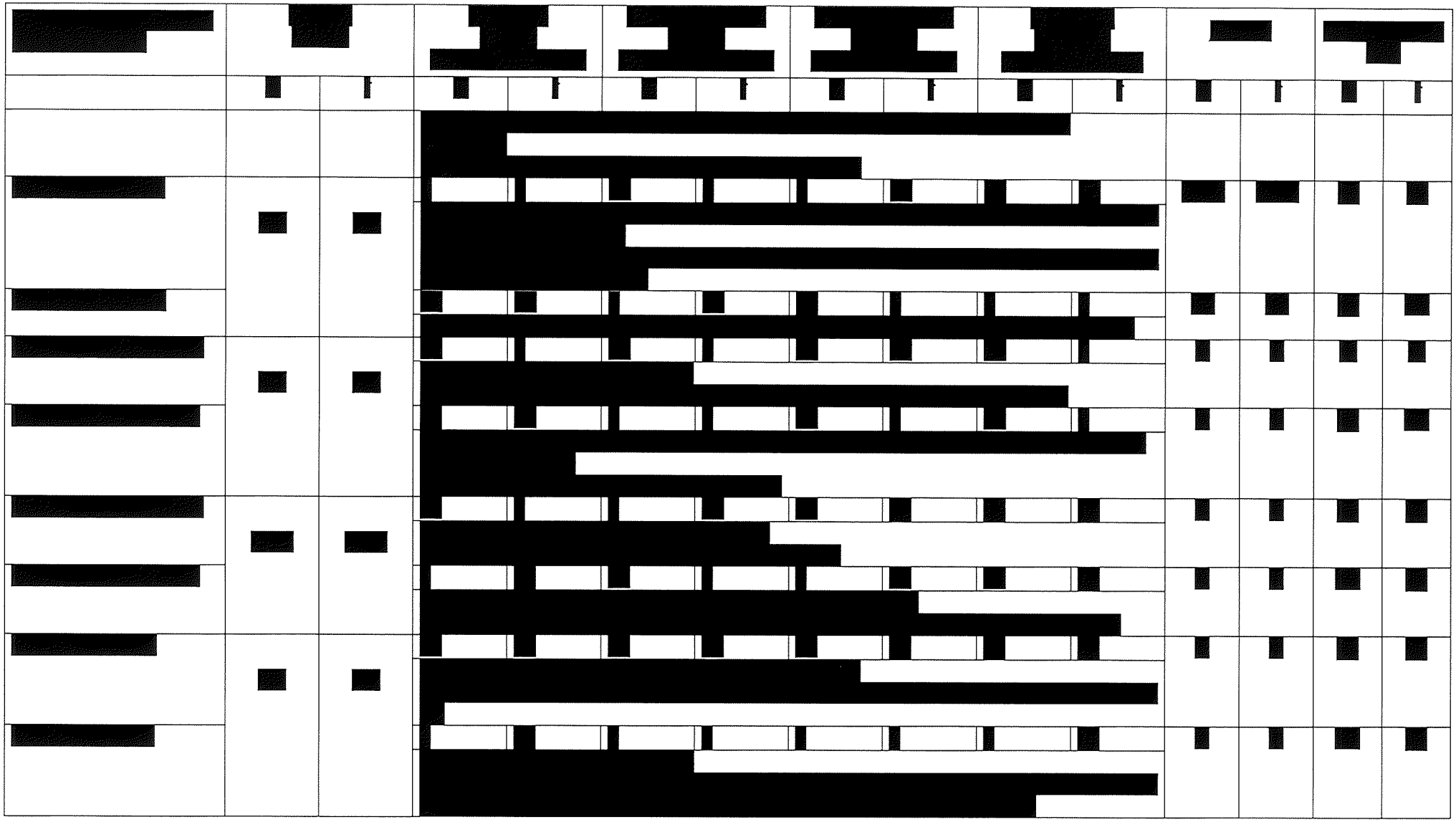
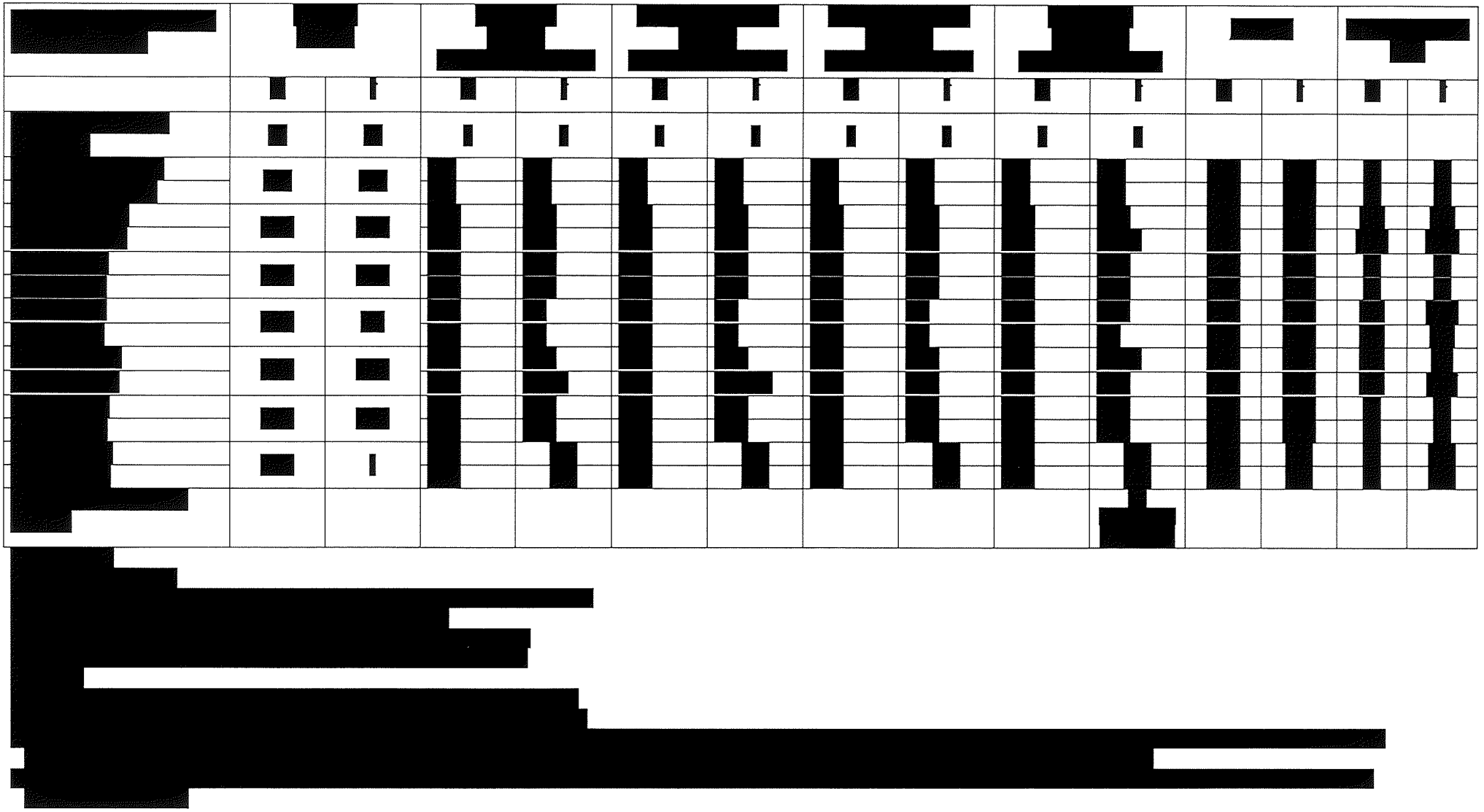
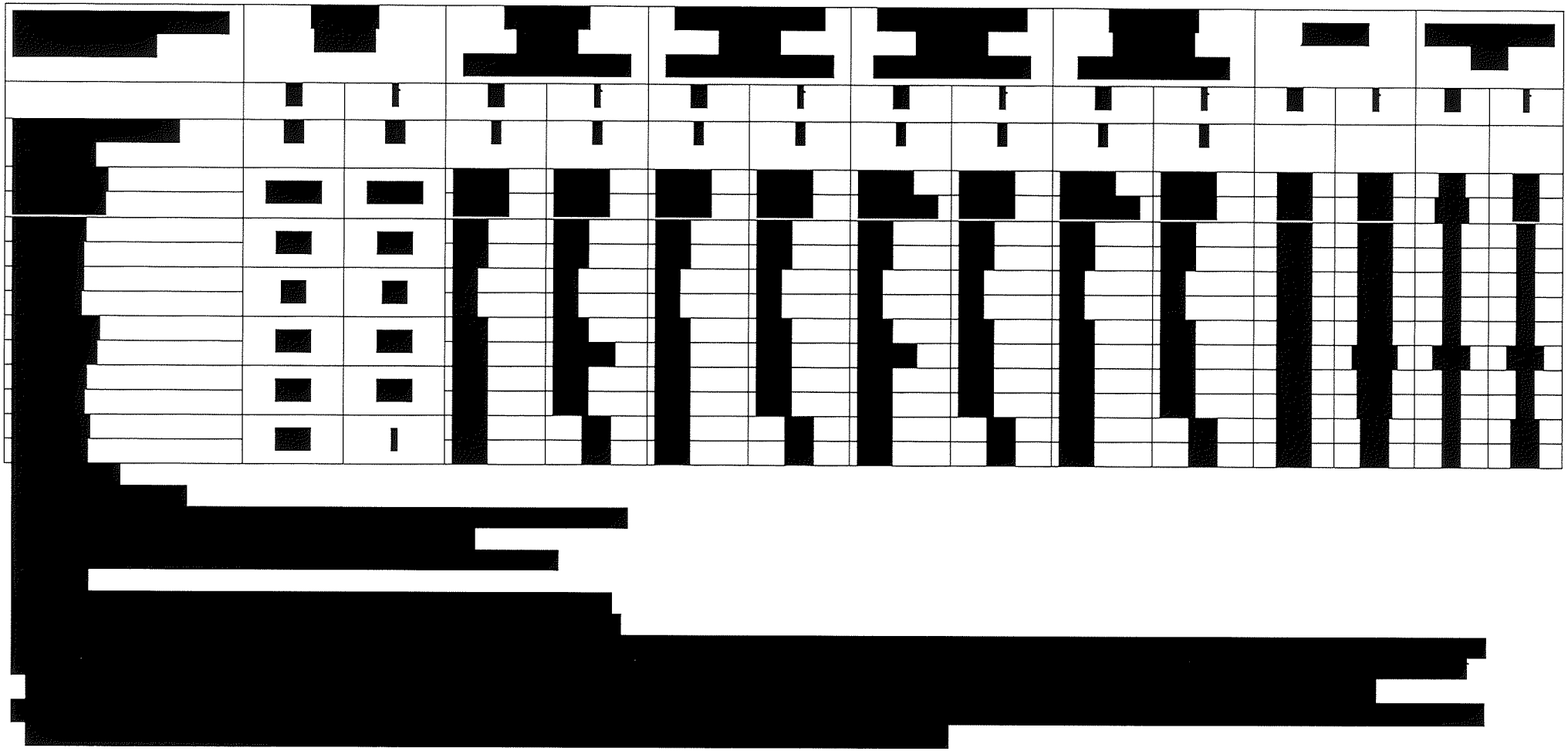


Table A6.4.1/01-2: Organ weights in rat subjected to varying concentration of Iodine (I_2) or Iodide (I^-) on their drinking water of 100 days



[redacted]

Table A6.4.1/01-3: Organ weights as a percentage of body weight in rat subjected to varying concentration of Iodine (I_2) or Iodide (I^-) on their drinking water of 100 days



Section A6.4.1/02 Annex Point IIA, VI.6.4.1	Subchronic oral toxicity, 2nd Species (dog)	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [X]	Technically not feasible [ ] Scientifically unjustified [ ]	
Limited exposure [ ]	Other justification [X]	
Detailed justification:	[redacted]	
	Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	[redacted]	
Evaluation of applicant's justification	[redacted]	
Conclusion	[redacted]	
Remarks		

Section A6.4.2 Subchronic dermal toxicity test

Annex Point
IIA VI.6.4

	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [X]	Technically not feasible [ ] Scientifically unjustified [ ]	
Limited exposure [ ]	Other justification [X]	
Detailed justification:	[redacted]	

Evaluation by Competent Authorities

EVALUATION BY RAPPORTEUR MEMBER STATE

Date	[redacted]
Evaluation of applicant's justification	[redacted]
Conclusion	[redacted]
Remarks	

Section A6.4.3 Subchronic inhalation toxicity test

Annex Point IIA VI.6.4

	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [X]	Technically not feasible [ ] Scientifically unjustified [ ]	
Limited exposure [ ]	Other justification [X]	
Detailed justification:	[redacted]	

Evaluation by Competent Authorities	
EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	[redacted]
Evaluation of applicant's justification	[redacted]
Conclusion	[redacted]
Remarks	

Section A6.5 Chronic

Oral

Annex Point IIA VI.6.5

	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [X]	**Technically not feasible [ ]** **Scientifically unjustified [ ]**	
Limited exposure [ ]	**Other justification [X]**	
Detailed justification:	[redacted]	
	Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	[redacted]	
Evaluation of applicant's justification	[redacted]	
Conclusion	[redacted]	
Remarks		

Section A6.6.1/01 *In-vitro* gene mutation in bacteria

Annex Point IIA, VI.6.6.1 Ames test

[redacted]

Official use only

1 REFERENCE

1.1	**Reference**	Thompson, P.W. (2002): Iodine: Reverse Mutation Assay "Ames Test" using Salmonella typhimurium; SafePharm Laboratories Ltd., Project No. 1580/003 (unpublished); [redacted]
1.2	**Data protection**	[redacted]
1.2.1	Data owner	[redacted]
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] Directive 2000/32/EC, Method B13/14; OECD Guideline 471
2.2	**GLP**	[redacted]
2.3	**Deviations**	[redacted]

3 MATERIALS AND METHODS

3.1	**Test material**	Iodine
3.1.1	Lot/Batch number	[redacted]
3.1.2	Specification	[redacted]
3.1.3	Description	[redacted]
3.1.4	Purity	[redacted]
3.1.5	Stability	[redacted]
3.2	**Study Type**	Bacterial reverse mutation test
3.2.1	Organism/cell type	Experiment 1 and 2: S. typhimurium: TA 1535, TA 1537, A 98, TA 100, TA 102

Section A6.6.1/01 ***In-vitro* gene mutation in bacteria**
Annex Point IIA, VI.6.6.1 Ames test

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	Plate incorporation method [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]

Section A6.6.1/01 *In-vitro* gene mutation in bacteria

Annex Point IIA, VI.6.6.1 Ames test

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

[redacted]

5.2 Results and discussion

[redacted]

5.3 Conclusion Iodine is not mutagenic in bacterial cells under the condition of the test.

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]

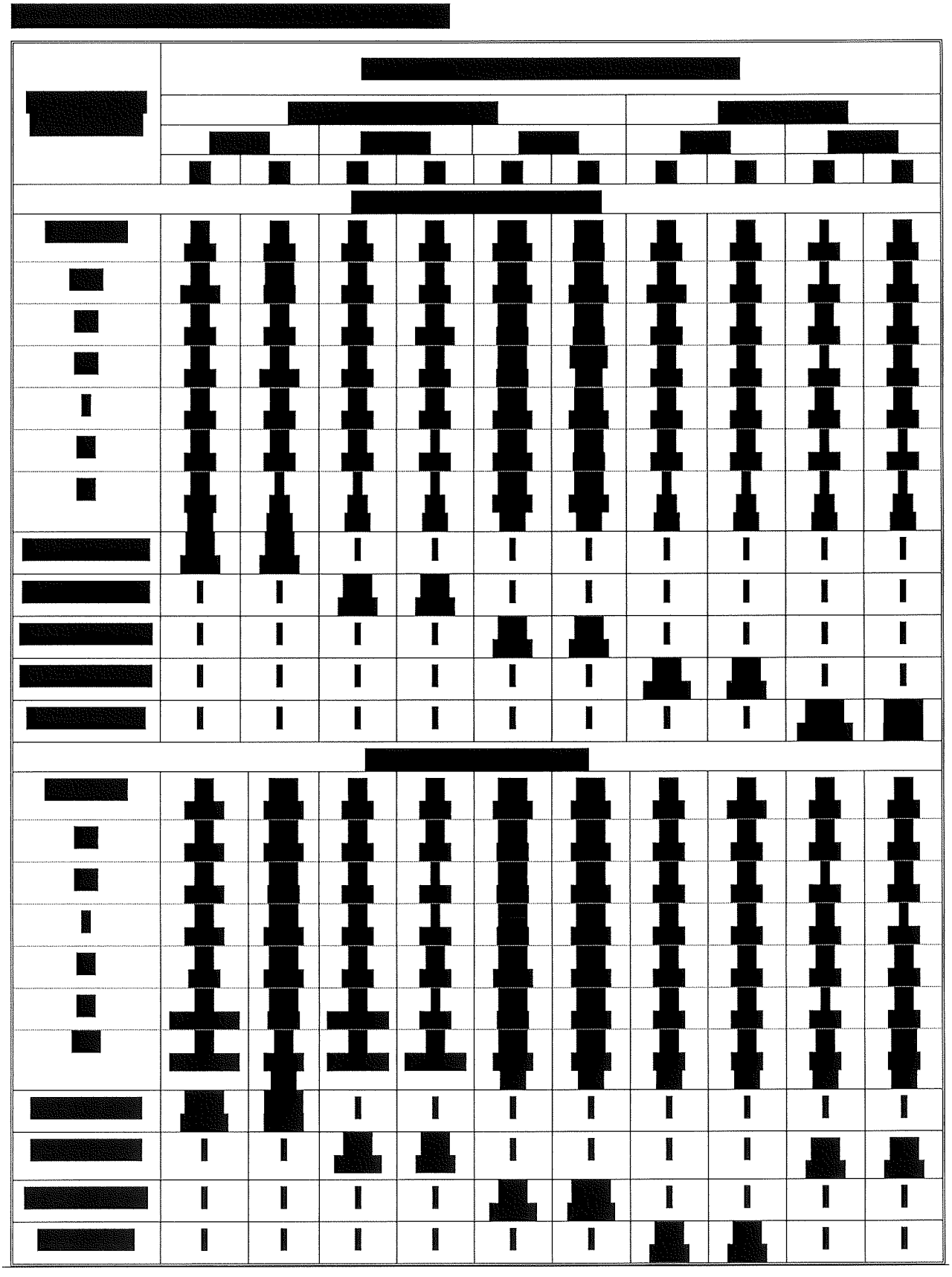
Reliability [redacted]

Acceptability [redacted]

Remarks [redacted]

Section A6.6.1/01 ***In-vitro* gene mutation in bacteria**

Annex Point IIA, VI.6.6.1 Ames test



Section A6.6.1/01 *In-vitro* gene mutation in bacteria

Annex Point IIA, VI.6.6.1 Ames test

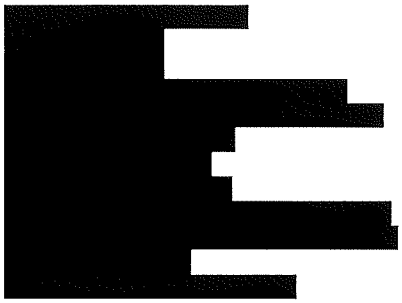
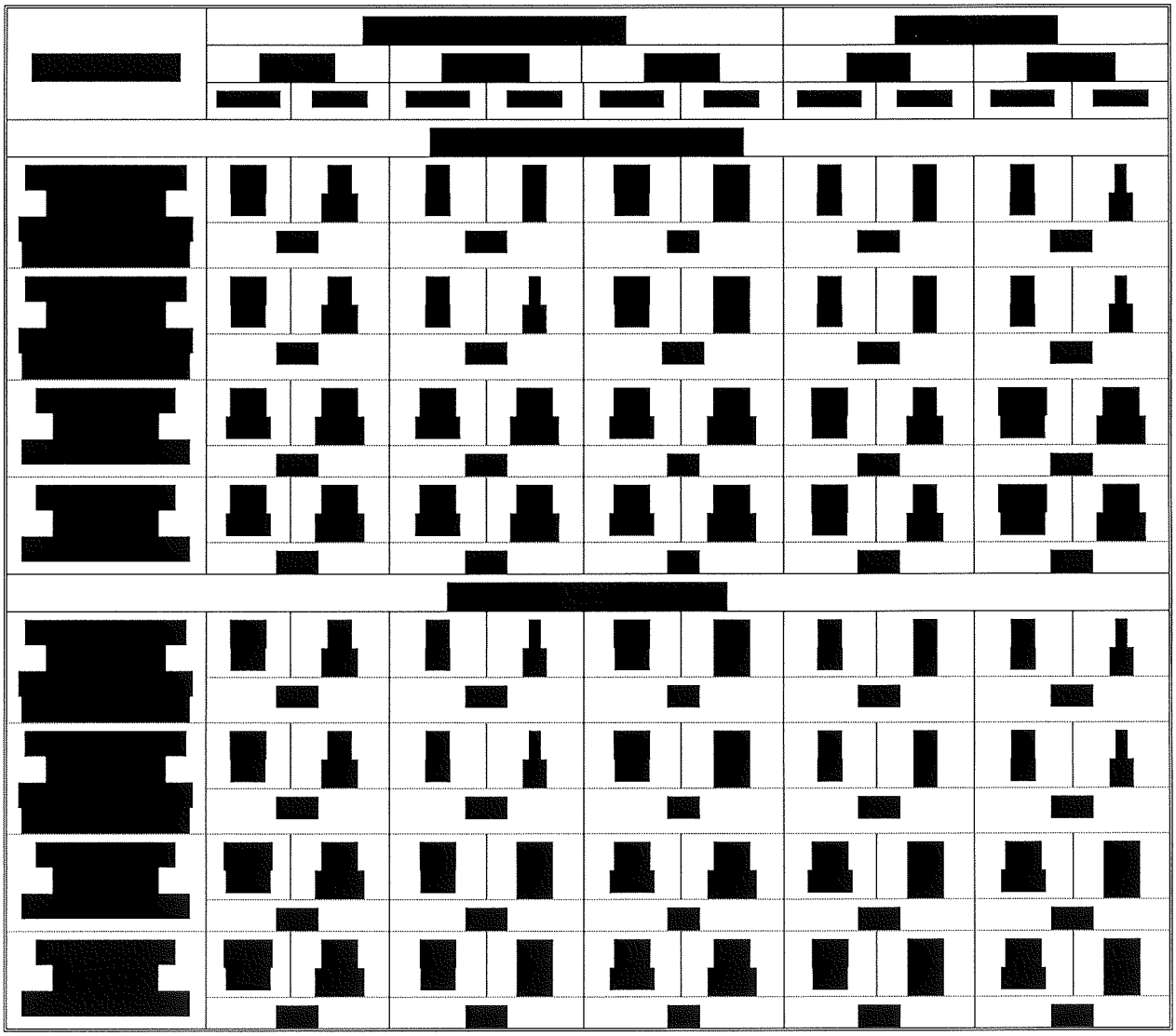


Table A6.6.1-2: Historical Data of Vehicle and Positive Control Values



Section A6.6.2/01 *In-vitro* cytogenicity in mammalian cells

Annex Point IIA6.6.1 / 6.6.2 / 6.6.3

Human Lymphocyte cells

[redacted]

Official use only

1 REFERENCE

1.1	**Reference**	Wright, N.P. (2002): Iodine: Chromosome Aberration Test in Human Lymphocytes In vitro. Safepharm Laboratories Ltd., SPL Project No. 1580/002 (unpublished); [redacted]
1.2	**Data protection**	[redacted]
1.2.1	Data owner	[redacted]
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] Directive 2000/32/EC, Method B10; OECD Guideline 473
2.2	**GLP**	[redacted]
2.3	**Deviations**	[redacted]

3 MATERIALS AND METHODS

3.1	**Test material**	Iodine
3.1.1	Lot/Batch number	[redacted]
3.1.2	Specification	[redacted]
3.1.3	Description	[redacted]
3.1.4	Purity	[redacted]
3.1.5	Stability	[redacted]
3.2	**Study Type**	In Vitro mammalian chromosome aberration test
3.2.1	Organism/cell type	[redacted]: Human Lymphocyte cells [redacted]

Section A6.6.2/01 *In-vitro* cytogenicity in mammalian cells

Annex Point IIA6.6.1 / 6.6.2 / 6.6.3

Human Lymphocyte cells

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	dissolved in culture medium
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 A6.6.2/01 *In-vitro* cytogenicity in mammalian cells

Annex Point IIA6.6.1 / 6.6.2 / 6.6.3

Human Lymphocyte cells

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]

Section A6.6.2/01 — ***In-vitro* cytogenicity in mammalian cells**

Annex Point IIA6.6.1 / 6.6.2 / 6.6.3 — Human Lymphocyte cells

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

[redacted]

Section A6.6.2/01 *In-vitro* cytogenicity in mammalian cells

Annex Point IIA6.6.1 / 6.6.2 / 6.6.3

Human Lymphocyte cells

5.2 Results and discussion

[redacted]

5.3 Conclusion

[redacted]. The test material was therefore considered to be clastogenic in human lymphocytes *in vitro* under these specific test conditions. Findings in the presence of metabolic activation are more relevant because they more resemble the *in vivo* situation. For the final assessment of the genotoxicity, the negative findings of *in vivo* studies are more relevant than this single *in vitro* finding.

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 A6.6.2/01 *In-vitro* cytogenicity in mammalian cells

Annex Point IIA6.6.1 / 6.6.2 / 6.6.3

Human Lymphocyte cells

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

Section A6.6.2 *In-vitro* cytogenicity in mammalian cells

Annex Point IIA6.6.1 / 6.6.2 / 6.6.3 Human Lymphocyte cells

Table A6.6.2/01-1. *In vitro* Test: Chromosomal Analysis without metabolic activation

Section A6.6.2 *In-vitro* cytogenicity in mammalian cells

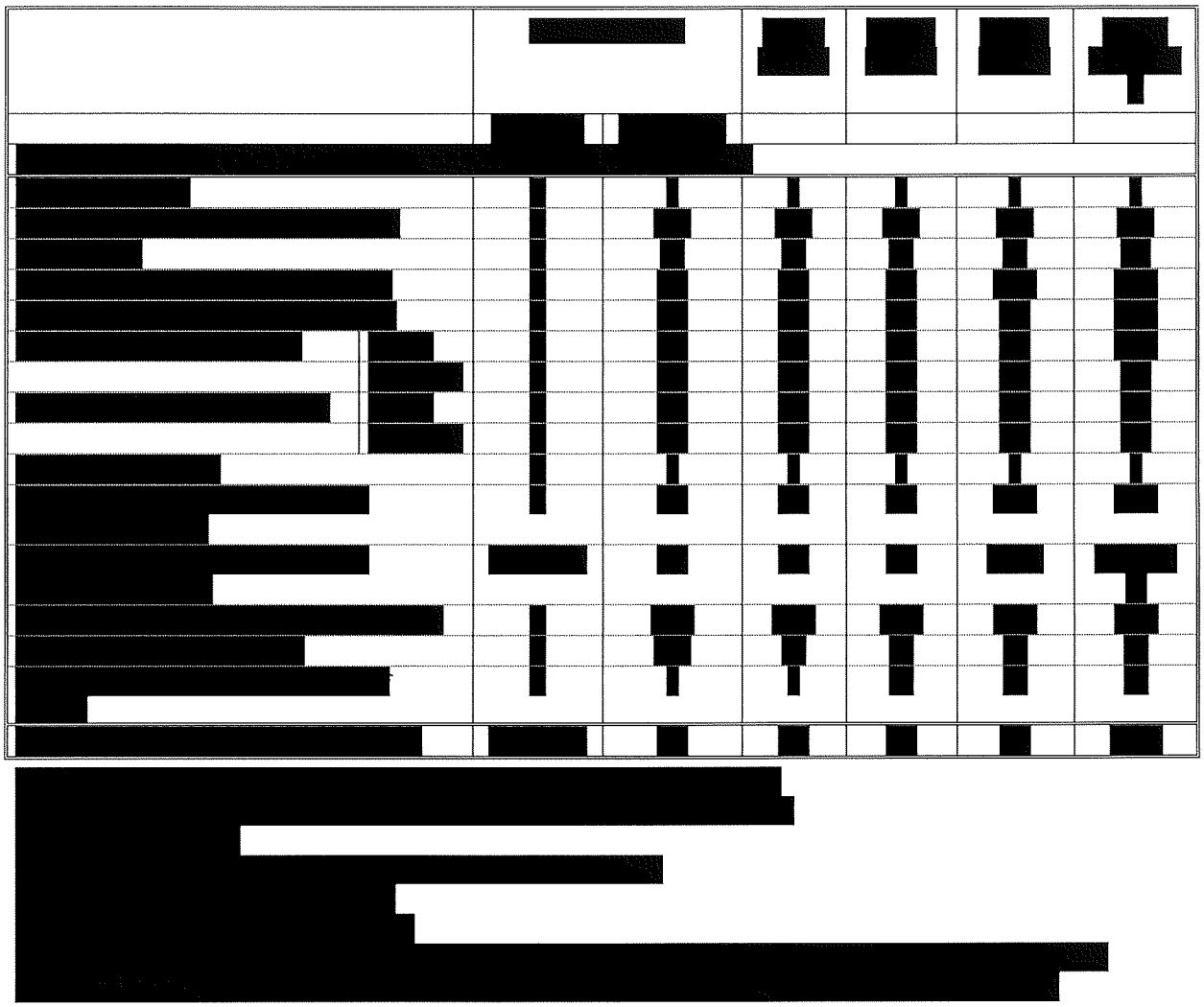
Annex Point IIA6.6.1 / 6.6.2 / 6.6.3 Human Lymphocyte cells

Table A6.6.2/01-2. *In vitro* Test: Chromosomal Analysis with metabolic activation

Section A6.6.2 *In-vitro* cytogenicity in mammalian cells

Annex Point IIA6.6.1 / 6.6.2 / 6.6.3 Human Lymphocyte cells

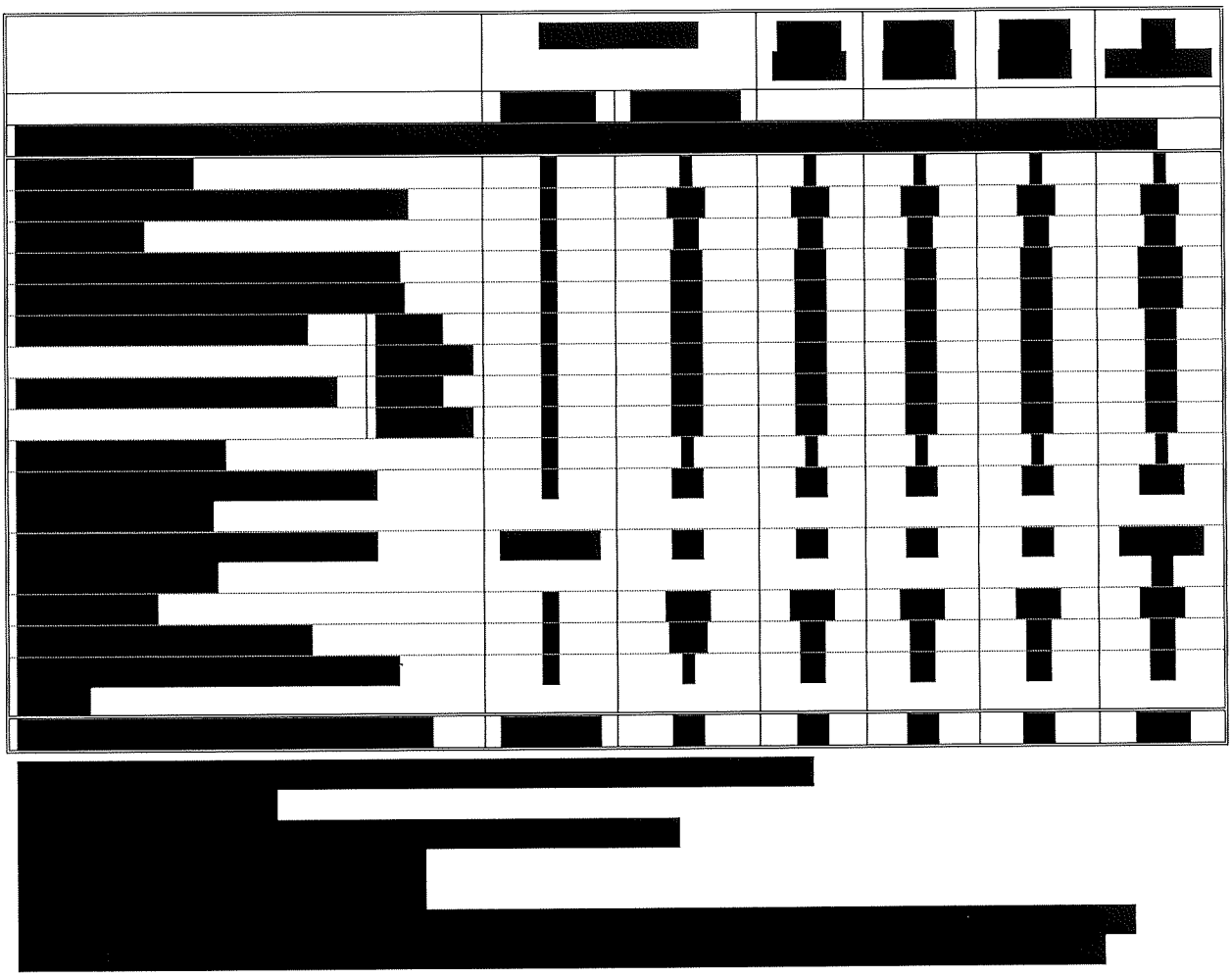
Table A6.6.2/01-3. *In vitro* Test: Chromosomal Analysis without metabolic activation



Section A6.6.2 *In-vitro* cytogenicity in mammalian cells

Annex Point IIA6.6.1 / 6.6.2 / 6.6.3 Human Lymphocyte cells

Table A6.6.2/01-4. ***In vitro*** **Test: Chromosomal Analysis with metabolic activation**



Section A6.6.3/01-04 *In-vitro* gene mutation in mammalian cells

Annex Point IIA VI.6.6.3 Mouse lymphoma assay

[redacted]

				Official use only
		1	**REFERENCE**	
1.1	Reference	[1]	Kessler, F.K., Laskin, D. L., Borzelleca, J.F., Carchman, R.A. (1980): Assessment of povidone-iodine using two in vitro assays; J. Environ. Pathol. & Toxicol. 4-2,3, pp. 327-335 Doc. No. 592-019 (published); Section A6.6.3/01	
		[2]	California Environmental Protection Agency, Department of Pesticide Regulation, Medical Toxicology Branch (2005), Summary of Toxicology Data, Iodine and related Iodine Complexes, p. 127; 213 http://www.cdpr.ca.gov/docs/toxsums/pdfs/718c.pdf Doc. No. 581-013 (published); Section A6.6.3/02	
		[3]	Expert Group on Vitamins and Minerals (2002): Revised Review of Iodine, p. 42 Doc. No. 681-001 (published); Section A6.6.3/03	
		[4]	Expert Group on Vitamins and Minerals (2003): Revised Review of Iodine, p. 206 Doc. No. 592-033 (published); Section A6.6.3/04	
1.2	**Data protection**	[redacted]		
1.2.1	Data owner	[redacted]		
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**	Yes OECD Guideline 476 was adopted in 1997. Mouse lymphoma assay, [redacted] Two of the references of OECD Guideline 476 are publications [redacted]		X1
2.2	**GLP**	[redacted]		
2.3	**Deviations**	Not applicable [redacted]		
		3	**MATERIALS AND METHODS**	
3.1	**Test material**	(1) Iodine (2) Potassium iodine (3) Polyvinylpyrrolidone iodine		