

**Acute Dermal Irritation/Corrosion**  
**with**  
**Niobium**

**Report**

**Version: Final**

**Date: 12 November 2009**

**BSL BIOSERVICE Study No.: 092569A**

**Sponsor:**

*CBMM Europe BV*  
*WTC H- Tower*  
*Zuidplein 96*  
*1077 XV, Amsterdam*  
*The Netherlands*

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für Gesundheitsschutz  
bei Arzneimitteln  
und Medizinprodukten  
ZLG-P-986.96.01

# 1. Copy of the GLP Certificate



**BAYERISCHES LANDESAMT  
FÜR GESUNDHEIT UND LEBENSMITTELSICHERHEIT,  
LANDESINSTITUT FÜR ARBEITSSCHUTZ UND PRODUKTSICHERHEIT  
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**GLP-Bescheinigung/Statement of GLP Compliance  
(gemäß/according to § 19b Abs. 1 Chemikaliengesetz)**

Eine GLP-Inspektion zur Überwachung der Einhaltung der GLP-Grundsätze gemäß Chemikaliengesetz bzw. Richtlinie 2004/9/EG wurde durchgeführt in:

Assessment of conformity with GLP according to Chemikaliengesetz and Directive 2004/9/EC at:

Prüfeinrichtung/Test facility       Prüfstandort/Test site

**BSL Bioservice Scientific Laboratories GmbH  
Behringstrasse 6 - 8  
82152 Planegg**

(Unverwechselbare Bezeichnung und Adresse/Unequivocal name and address)

**Prüfungen nach Kategorien/Areas of Expertise**  
(gemäß/according ChemVwV-GLP Nr. 5.3/OECD guidance)

**2 Prüfungen auf toxikologische Eigenschaften  
3 Prüfungen auf mutagene Eigenschaften  
9 Sonstige Prüfungen:**

**a) Mikrobiologische Sicherheitsprüfungen  
b) Wirksamkeitsprüfungen an Zellkulturen**

**Datum der Inspektion/Date of Inspection**  
(Tag/Monat/Jahr/day/month/year)

**16./17.09.2008**

Die/Der genannte Prüfeinrichtung/Prüfstandort befindet sich im nationalen GLP-Überwachungsverfahren und wird regelmäßig auf Einhaltung der GLP-Grundsätze überwacht.

The above mentioned test facility/test site is included in the national GLP Compliance Programme and is inspected on a regular basis.

Auf der Grundlage des Inspektionsberichtes wird hiermit bestätigt, dass in dieser Prüfeinrichtung/diesem Prüfstandort die oben genannten Prüfungen unter Einhaltung der GLP-Grundsätze durchgeführt werden können.

Based on the inspection report it can be confirmed, that this test facility/test site is able to conduct the aforementioned studies in compliance with the Principles of GLP.

München, 06.04.2009

Ritter  
Leitender Gewerbedirektor



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## 4. Preface

### 4.1. Abbreviations

BGBI.	Bundesgesetzblatt
GLP	Good Laboratory Practice
OECD	Organisation of Economic Cooperation and Development
QA	Quality Assurance
QAU	Quality Assurance Unit
SOP	Standard Operating Procedures

#### 4.2. *General*

Sponsor: CBMM Europe BV  
WTC H- Tower  
Zuidplein 96  
1077 XV, Amsterdam  
The Netherlands

Study Monitor: Mr Jorge Davo  
CBMM  
Companhia Brasileira de Metalurgia  
e Mineração  
Córrego da Mata s/n  
38183-903 Araxá - MG  
Brasil

Test Facility: BSL BIOSERVICE  
Scientific Laboratories GmbH  
Behringstraße 6/8  
82152 Planegg  
Germany

BSL BIOSERVICE Study No.: 092569A

Test Item: Niobium

Title: Acute Dermal Irritation/Corrosion  
with Niobium

#### 4.3. *Project Staff*

Study Director: Dr. Anne Laure Leoni  
Deputy Study Director: Dr. Daniela Stelter  
Management: Dr. Wolfram Riedel  
Dr. Angela Lutterbach

Head of  
Quality Assurance Unit: Dipl.-Biol. Uwe Hamann

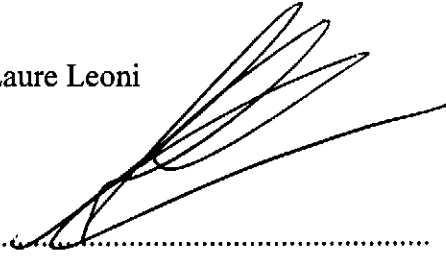
#### 4.4. *Schedule*

Arrival of the Test Item: 20 July 2009  
Date of Draft Study Plan: 31 July 2009  
Date of Final Study Plan: 06 August 2009  
Start of Experiment: 07 September 2009  
End of Experiment: 11 September 2009  
Date of Draft Report: 25 September 2009  
Date of Final Report: 12 November 2009

## 5. Project Staff Signatures

Study Director


Dr. Anne Laure Leoni



.....

Date: 12 Nov 2009  
.....

Management



.....

Print name: Dr. Angela Lutterbach

Date: 12 Nov 2009  
.....



## 6. Quality Assurance

### 6.1. GLP Compliance

This study was conducted to comply with:

Chemikaliengesetz (“Chemicals Act”) of the Federal Republic of Germany, Appendix 1 to § 19a as amended and promulgated on June 20, 2002 (BGBl. I Nr. 40 S. 2090), revised October 31, 2006 (BGBl. I Nr. 50 S. 2407).

OECD Principles of Good Laboratory Practice (as revised in 1997); OECD Environmental Health and Safety Publications; Series on Principles of Good Laboratory Practice and Compliance Monitoring - Number 1. Environment Directorate, Organisation for Economic Co-operation and Development, Paris 1998.

This study was assessed for compliance with the study plan and the Standard Operating Procedures of BSL BIOSERVICE. The study and/or the test facility were periodically inspected by the Quality Assurance unit according to the corresponding SOPs. These inspections and audits were carried out by the Quality Assurance unit, personnel independent of staff involved in the study. A signed Quality Assurance Statement, listing all performed audits, is included in the report.

### 6.2. Guidelines

This study followed the procedures indicated by internal BSL BIOSERVICE SOPs and the following internationally accepted guidelines and recommendations:

First Addendum to OECD Guidelines for Testing of Chemicals, Section 4, No. 404, “Acute Dermal Irritation/Corrosion” adopted 24 April 2002

Commission Regulation (EC) No 440/2008, L 142, Annex Part B, 30 May 2008

EPA Health Effects Test Guidelines, OPPTS 870.2500 “Acute dermal irritation”, EPA 712-C-98-196, (August 1998)

### 6.3. Archiving

The following records will be stored in the scientific archives of BSL BIOSERVICE Scientific Laboratories GmbH according to the GLP Regulations:

A copy of the final report, the study plan and a documentation of all raw data generated during the conduct of the study (documentation forms as well as any other notes of raw data, printouts of instruments and computers) and the correspondence with the Sponsor concerning the study.

If test item is left, a sample will be stored according to the period fixed by the GLP Regulations. Samples that are unstable may be disposed of before that time. No raw data or material relating to the study will be discarded without the Sponsor's prior consent. Unless otherwise agreed upon, the remaining test item will be discarded three months after the release of the report.

## 7. Statement of Compliance

BSL BIOSERVICE-  
Study No.: 092569A  
Test Item: Niobium  
Title: Acute Dermal Irritation/Corrosion  
with Niobium  
Study Director: Dr. Anne Laure Leoni

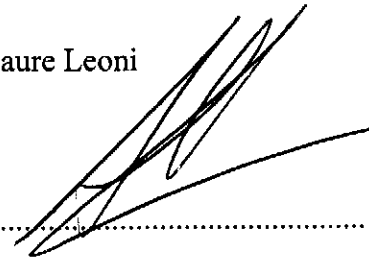
This study performed in the test facility BSL BIOSERVICE Scientific Laboratories GmbH was conducted in compliance with Good Laboratory Practice Regulations:

Chemikaliengesetz ("Chemicals Act") of the Federal Republic of Germany, Appendix 1 to § 19a as amended and promulgated on June 20, 2002 (BGBl. Nr. 40 S. 2090), revised October 31, 2006 (BGBl. I Nr. 50 S. 2407).

"OECD Principles of Good Laboratory Practice (as revised in 1997)", Paris 1998.

There were no circumstances that may have affected the quality or integrity of the study.

Study Director: Dr. Anne Laure Leoni



.....

Date: ..... 25 Nov 2003 .....

## 8. Statement of the Quality Assurance Unit

BSL BIOSERVICE-  
Study No.: 092569A  
Test Item: Niobium  
Title: Acute Dermal Irritation/Corrosion  
with Niobium  
Study Director: Dr. Anne Laure Leoni

This report was audited by the Quality Assurance Unit and the conduct of this study was inspected on the following dates:

<i>Phases of QAU Inspections</i>	<i>Dates of QAU Inspections</i>	<i>Dates of Reports to the Study Director and Management</i>
Audit Final Study Plan:	11 August 2009	11 August 2009
Audit Experimental Phase (Method Audit):	03 June 2009	03 June 2009
Audit Final Report:	17 November 2009	17 November 2009

This report reflects the raw data.

Member of the  
Quality Assurance Unit:

*Anne Krabiell*

Print name: Dipl.oec.troph (FH)  
Anne Krabiell

Date: *23 Nov 2009*

## 9. Summary

On the basis of the test results given below and in conformity with the criteria given in Annex VI to Commission Directive 2001/59/EC as well as in Annex I of Regulation (EC) 1272/2008, the substance should be:

classified as corrosive     [  ]  
classified as irritant        [  ]  
not classified                [  ]

Species/strain:                New Zealand White Rabbits CrI: KBL (NZW)  
Number of animals:            3  
Duration of exposure:         4 hours  
Amount of substance:         0.5 g per test site  
Type of dressing:             occlusive [  ]     semi-occlusive [  ]  
Vehicle (moistening):         Aqua ad injectionem  
First time of effects:         no effects observed  
Last time of effects:         no effects observed  
Reversibility of the  
observed effects:             no effects observed  
  
Method:                         OECD 404  
                                  EC 440/2008  
                                  OPPTS 870.2500

**Table 1: Average Scores – (24, 48, 72 Hour Reading)**

<i>Mean value irritation scores</i>		
<i>Mean 24 – 72 hours</i>		
<i>Animal number</i>	<i>Erythema</i>	<i>Oedema</i>
1	0	0
2	0	0
3	0	0
<b>Total mean value</b>	<b>0</b>	<b>0</b>

### 9.1. Conclusions

Under the conditions of the present study, single dermal application of the test item Niobium to rabbits at a dose of 0.5 g showed neither irritant nor corrosive effects.

Neither mortalities nor significant clinical signs of toxicity were observed.

In conformity with the EC criteria for classification and labelling requirements for dangerous substances and preparations according to Annex VI of Commission Directive 2001/59/EC and Annex I of Regulation (EC) 1272/2008, the test item Niobium does not have to be classified and has no obligatory labelling requirement for skin irritation (for details see *Evaluation of Results*).

## 10. Aim of the Study

### 10.1. Justification for Selection of the Test System

The test for acute dermal irritation/corrosion is performed on the rabbit.

Test items meeting any of the following criteria will not be tested:

- a) materials that have predictable corrosive potential based on structure-activity relationships and/or physicochemical properties such as strong acidity or alkalinity, e.g., when the material to be applied has a pH of 2 or less or 11.5 or greater
- b) materials which have been proved to be highly toxic by the dermal route
- c) materials which, in an acute dermal toxicity test, have been shown not to produce irritation of the skin at the limit test dose level of 2000 mg/kg body weight
- d) materials which have been proved to be corrosive by the *in-vitro* skin corrosion test

### 10.2. Justification for Selection of the Test Method

No validated stand-alone *in vitro* method is available for assessing acute dermal irritation.

## 11. Materials and Methods

### 11.1. Characterisation of the Test Item

The test item and the information concerning the test item were provided by the Sponsor. All data related to the test item are the responsibility of the Sponsor and have not been verified by the test facility.

Name:	Niobium
Product:	Niobium Metal (Nb)
CAS no.:	7440-03-1
Batch no.:	AD/4202
Chemical name:	niobium
Density:	~8.5 g / cm <sup>3</sup>
Active components:	Nb - >98.5%
Colour:	silver grey metallic
Physical state:	solid
Storage:	at room temperature
Stability:	stable
Safety precautions:	Routine hygienic procedures were sufficient to assure personnel health and safety.

### 11.2. Preparation of the Test Item

The test item was used as delivered by the sponsor.

In order to ensure good skin contact, it was moistened with Aqua ad injectionem (Braun, Batch. 7494A191, expiry date: November, 2010).

### 11.3. Vehicle

Aqua ad injectionem (Braun, Batch. 7494A191, expiry date: November, 2010).

This vehicle was chosen due to its non-irritating characteristics.

### 11.4. Weight-of-the-evidence Analysis

In order to avoid the unnecessary use of animals and to minimise any testing that is likely to produce severe responses in animals, a weight-of-the-evidence analysis was performed with the available data (data from the test substance data sheet and existing human and animal data found with the same active ingredient). The paperwork is archived in the project file. Additionally the confirmation in writing that the studies are required for submission to regulatory authorities or to fulfil obligations postulated by law was taken into account.



### 11.5. Test System

Species/strain: Healthy New Zealand White Rabbits, Crl: KBL (NZW)

Source: Charles River Deutschland, D-97633 Sulzfeld

Sex: female

Body weight at the beginning of the study: > 2 kg

Age at the beginning of the study: approximately 15 weeks old

Number of animals: 3

The animals were derived from a controlled full barrier maintained breeding system (SPF). According to Art. 9.2, No.7 of the German Act on Animal Welfare the animals were bred for experimental purposes.

#### 11.5.1. Housing and Feeding Conditions

- Semi-barrier in an air-conditioned room
- Temperature:  $18 \pm 3^{\circ}\text{C}$  (recommendations of TVT, GV-SOLAS; see References)
- Relative humidity:  $55 \pm 10\%$
- Artificial light, sequence being 12 hours light, 12 hours dark
- Air change: at least 10 x / hour
- Free access to autoclaved hay and to Altromin 2123 maintenance diet for rabbits (lot no. 1306), rich in crude fibre
- Free access to tap water (drinking water, municipal residue control, microbiol. controlled periodically)
- Certificates of food, water and bedding are filed at BSL BIOSERVICE
- Housed in ABS - plastic rabbit cages, floor  $4200 \text{ cm}^2$
- Adequate acclimatisation period (at least 5 days)

#### 11.6. Preparation of the Animals

Approximately 24 hours before the test, the fur was removed from the dorsal area of the trunk by using an electric clipper. Care was taken to avoid abrading the skin, and only animals with healthy intact skin were used.

#### 11.7. Initial Test (in vivo Dermal Irritation/Corrosion Test using one Animal)

The test item was not expected to produce corrosion but might be irritating. Therefore, a single patch was applied to one animal for 4 hours.

### 11.8. Application

The test item was applied first to a gauze patch at a single dose. To ensure good skin contact, it was moistened with Aqua ad injectionem. The patch was then applied to the skin on a small area (approx. 6 cm<sup>2</sup>) on the left side of the dorsal area. The gauze was held in place with non-irritating tape. The untreated right side served as control. The patch was fixed with a semi-occlusive dressing. The limits of the application site were marked with an ink marker.

### 11.9. Dose Level

A dose of 0.5 g of the test item was applied to each test site.

### 11.10. Exposure Period

The test item was held in contact with the skin throughout a 4-hour period.

At the end of the exposure period, the residual test item was not removed.

### 11.11. Confirmatory Test

The results of the initial test did not indicate the test item to be corrosive or a severe irritant to the skin using the procedure described. In order to confirm the response, two additional animals were treated in the same manner.

### 11.12. Observation Period

All animals were observed for 72 hours after the patch removal.

### 11.13. Clinical Observation

For the determination of classification-relevant values, the animals were examined for signs of erythema and oedema at 1 hour as well as 24, 48 and 72 hours after patch removal. Dermal irritation was scored and recorded according to the grades in the table below (Table 2). Any other signs such as hyperplasia, scaling, discoloration, fissures and scabs or any systemic effects were also recorded.

For the initial test in one animal, the test site was also examined immediately after the patch has been removed.

**Table 2: Scoring System**

<i>Erythema and eschar formation</i>	
No erythema	0
Very slight erythema (barely perceptible)	1
Well defined erythema	2
Moderate to severe erythema	3
Severe erythema (beef-redness) to eschar formation preventing grading of erythema	4
<i>Oedema formation</i>	
No oedema	0
Very slight oedema (barely perceptible)	1
Slight oedema (edges of area well defined by definite raising)	2
Moderate oedema (raised approximately 1 mm )	3
Severe oedema (raised more than 1 mm and extending beyond exposure area)	4

#### 11.14. Evaluation of Results

Individual reactions of each animal were recorded at each time of observation.

Nature, severity and duration of all lesions observed were described.

Body weights were recorded at the start and at the end of the study.

On the basis of the test results, the test substance was classified in any of the following classes in conformity with the criteria given in Annex VI to Commission Directive 2001/59/EC:

- **Corrosive** and assigned the symbol „C“ and the indication of danger corrosive in accordance with the following criteria:
  - a substance or a preparation is considered to be corrosive if, when it is applied to healthy intact animal skin, it produces full thickness destruction of skin tissue on at least one animal during the test for skin irritation cited in Annex B.4 to Commission Regulation (EC) No. 440/2008, L 142 or during an equivalent method,
  - classification can be based on the results of a validated in vitro test, such as that cited in Annex B.40 to Commission Regulation (EC) No. 440/2008, L 142 (skin corrosion: rat skin transcutaneous electrical resistance assay and human skin model assay),

- a substance or a preparation should also be considered corrosive if the result can be predicted, for example from strongly acid or alkaline reactions indicated by a pH of 2 or less or 11.5 or greater. However, where extreme pH is the basis for classification, acid/alkali reserve may also be taken into consideration. If consideration of alkali/acid reserve suggests the substance or preparation may not be corrosive then further testing should be carried out to confirm this, preferably by use of an appropriate validated in vitro test. Consideration of acid/alkali reserve should not be used alone to exonerate substances or preparations from classification as corrosive.

Risk phrases shall be assigned in accordance with the following criteria:

*R35 Causes severe burns*

- if, when applied to healthy intact animal skin, full thickness destruction of skin tissue occurs as a result of up to three minutes exposure, or if this result can be predicted.

*R34 Causes burns*

- if, when applied to healthy intact animal skin, full thickness destruction of skin tissue occurs as a result of up to four hours exposure, or if this result can be predicted,
- organic hydroperoxides, except where evidence to the contrary is available.

Notes:

Where classification is based on results of a validated in vitro test R35 or R34 should be applied according to the capacity of the test method to discriminate between these.

Where classification is based upon consideration of extreme pH alone, R35 should be applied.

- ***Irritant*** and assigned the symbol „Xi“ and the indication of danger „irritant“ in accordance with the criteria given below.

The following risk phrase shall be assigned in accordance with the criteria given:

*R38 Irritating to skin*

- Substances and preparations which cause significant inflammation of the skin which persists for at least 24 hours after an exposure period of up to four hours determined on the rabbit according to the cutaneous irritation test method cited in Annex B.4 to Commission Regulation (EC) No. 440/2008, L 142 (skin corrosion).

Inflammation of the skin is significant if:

- (a) the mean value of the scores for either erythema and eschar formation or oedema formation, calculated over all the animals tested, is 2 or more; or
- (b) in the case where the Annex B.4 (skin corrosion) test has been completed using three animals, either erythema and eschar formation or oedema formation equivalent to a mean value of 2 or more calculated for each animal separately has been observed in two or more animals.

In both cases all scores at each of the reading times (24, 48 and 72 hours) for an effect should be used in calculating respective mean values.

Inflammation of the skin is also significant if it persists in at least two animals at the end of the time of observation. Particular effects e.g. hyperplasia, scaling, discoloration, fissures, scabs and alopecia should be taken into account. Relevant data may also be available from non-acute animal. These are considered significant if the effects seen are comparable to those described above.

- Substances and preparations which cause significant inflammation of the skin, based on practical observations in humans on immediate, prolonged or repeated contact.
- Organic peroxides, except where evidence to the contrary is available.

On the basis of the test results, the following risk phrases shall be assigned in conformity with the criteria given in Annex I of Regulation (EC) 1272/2008:

*Skin corrosion, category 1 A, B, C:*

Destruction of skin tissue, with subcategorisation based on exposure of up to 3 minutes (A), 1 hour (B), or 4 hours (C). DANGER, corrosion symbol in diamond. Causes severe skin burns and eye damage.

*Skin irritation, category 2:*

Mean value of  $\geq 2.3 \leq 4.0$  for erythema / eschar or edema in at least 2 of 3 tested animals from gradings at 24, 48, and 72 hours (or on 3 consecutive days after onset if reactions are delayed); inflammation that persists to end of the (normally 14-day) observation period in at least 2 animals, particularly taking into account alopecia (limited area), hyperkeratosis, hyperplasia, and scaling; in some cases where there is pronounced variability of response among animals, with very definite positive effects related to chemical exposure in a single animal but less than the criteria above. WARNING, exclamation mark in diamond. Causes skin irritation.

## **12. Deviations from the Study Plan**

There was no deviation from the study plan.



**Table 4: Individual Data**

<i>Individual systemic and local findings</i>									
<i>Time after patch removal</i>	<i>Animal number 1</i>			<i>Animal number 2</i>			<i>Animal number 3</i>		
	<i>systemic findings</i>	<i>specific local findings</i>	<i>comments</i>	<i>systemic findings</i>	<i>specific local findings</i>	<i>comments</i>	<i>systemic findings</i>	<i>specific local findings</i>	<i>comments</i>
1 hour	nsf	nsf	-	nsf	nsf	-	nsf	nsf	-
24 hours	nsf	nsf	-	nsf	nsf	-	nsf	nsf	-
48 hours	nsf	nsf	-	nsf	nsf	-	nsf	nsf	-
72 hours	nsf	nsf	-	nsf	nsf	-	nsf	nsf	-

nsf = no specific findings

**13.1. Body Weight Development**

There were no significant body weight changes during the contact and observation period (Table 5).

**Table 5: Absolute Body Weights in kg**

<i>Animal number</i>	<i>Start of study (weight kg)</i>	<i>End of study (weight kg)</i>
1	3.3	3.4
2	3.2	3.3
3	3.5	3.5



### 13.2. Conclusions

Under the conditions of the present study, single dermal application of the test item Niobium to rabbits at a dose of 0.5 g showed neither irritant nor corrosive effects.

Neither mortalities nor significant clinical signs of toxicity were observed.

In conformity with the EC criteria for classification and labelling requirements for dangerous substances and preparations according to Annex VI of Commission Directive 2001/59/EC and Annex I of Regulation (EC) 1272/2008, the test item Niobium does not have to be classified and has no obligatory labelling requirement for skin irritation (for details see *Evaluation of Results*).

## 14. Distribution of the Report

1 original (paper):	Sponsor
1 copy (paper):	BSL Bioservice
1 copy (electronic):	Sponsor

## 15. References

BSL BIOSERVICE, Standard Operating Procedures (SOP) No. 11-2-1

Commission Regulation (EC) No 440/2008, L 142, Annex Part B of 30 May 2008 laying down test methods pursuant to Regulation (EC) No. 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH)

EC, 2001: Commission Directive 2001/59/EC of 6th August 2001 adapting to technical progress for the 28th time Council Directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions relating to the Classification, Packaging and Labelling of Dangerous Substances. Official Journal of the European Communities, L 225, August 21, 2001

Merkblatt zur tierschutzgerechten Haltung von Versuchstieren; Merkblatt 55 Kaninchen; TVT Tierärztliche Vereinigung für Tierschutz




OECD Guidelines for Testing of Chemicals  
Section 4: Health Effects, No. 404  
Acute Dermal Irritation/Corrosion (2002)  
Organisation for Economic Co-Operation and Development, Paris

Planung, Struktur von Versuchstierbereichen tierexperimentell tätiger Institutionen; Veröffentlichung GV-SOLAS (Gesellschaft für Versuchstierkunde, Society for Laboratory Animal Science), Mai 1988

Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No. 1907/2006. Official Journal of the European Communities, L 353, 31.12.2008

US-EPA, 1998 Acute Dermal Irritation. Health Effects Test Guidelines, OPPTS 870.2500. United States, Environmental Protection Agency, Prevention, Pesticides and Toxic Substances (7101) EPA 712-C-98-196 (August 1998)

## 16. Appendix - Certificate of Analysis

 <b>COMPANHIA BRASILEIRA DE METALURGIA E MINERAÇÃO</b> Córrego da Mata S/N - C.P. 08 - Araxá - Minas Gerais - Cep: 38.183-970 - Brazil Phone: (55-34) 3869-3000 - Facsimile: (55-34) 3869-3300			
CERTIFICATE OF ANALYSIS		NUM.	DATE
PRODUCT NIOBIUM METAL	LOT AD/4202 ✓	QUANTITY 7.0	07/06/2009
MARK	CUSTOMER REACH	PACKAGING 1/1	
Element	Analysis		
ppm Al	<10		
ppm Be	<1		
ppm C	<30		
ppm Co	<1		
ppm Cr	<10		
ppm Cu	<1		
ppm Fe	<10		
ppm H	14		
ppm Hf	<25		
ppm Mo	<90		
ppm N	23		
ppm Ni	<20		
ppm O	89		
ppm S	<10		
ppm Si	<20		
ppm Ta	1267		
ppm Ti	<13		
ppm W	<18		
ppm Zr	<7		
Size Distribution			
Screen (mm)	(% ) Analysis		
Observation			
Emitted by  // Leandro Oliveira Lima Chemist		Approved by  // Andreia Duarte Menezes Teixeira Lab. Manager	