# Elemental Impurities

## Inhalation grade Lactose (EU)

Product group: Inhalation

Brand name: Respitose®

Product description: Lactose Monohydrate
Lactose Anhydrous

Document No.: PD-0650 

Dear Customer,

In framework of the ICH Q3D (R2) guideline, DFE Pharma tested batches of Respitose®, originating from the production site located in Veghel, The Netherlands representing the brand name mentioned above.

Neither the elements listed below, nor other elements classified as class 2B, are intentionally added during the production process.

DFE Pharma performed analysis on relevant elemental impurities categorized as class 1, class 2A and some class 2B, class 3 and other relevant elements by the ICH Q3D (R2) guideline (according to table 5.1: Elements to be considered in the Risk Assessment – Oral Dosage Form).
Analysis was performed using the analysis technique ICP-MS (Inductively Coupled Plasma-Mass Spectrometry) conforming to USP-NF <233> and Ph. Eur. 2.4.20.

*Table 1: Table of elemental impurities following ICH Q3D (R2)*

| Metal | Class | Limit in ppm inhalation | Required for inhalation | Tested at DFE Pharma |
|---|---|---|---|---|
| Cadmium | 1 | 0.3 | Yes | Yes |
| Lead | 1 | 0.5 | Yes | Yes |
| Arsenic | 1 | 0.2 | Yes | Yes |
| Mercury | 1 | 0.1 | Yes | Yes |
| Cobalt | 2A | 0.3 | Yes | Yes |
| Vanadium | 2A | 0.1 | Yes | Yes |
| Nickel | 2A | 0.6 | Yes | Yes |
| Selenium | 2B | 13 | No | Yes |
| Lithium | 3 | 2.5 | Yes | Yes |
| Antimony | 3 | 2 | Yes | Yes |
| Barium | 3 | 30 | Yes | Yes |
| Molybdenum | 3 | 1 | Yes | Yes |
| Copper | 3 | 3 | Yes | Yes |
| Tin | 3 | 6 | Yes | Yes |
| Chromium | 3 | 0.3 | Yes | Yes |
| Aluminium | None | - | No | Yes |
| Strontium | None | - | No | Yes |

*[1]: Limits are based on option 1 of the ICH Q3D (R2) guidelines, based on administration of not more than 10g of drug product per day (stated in table A.2.2).

DFE Pharma GmbH & Co. KG
Klever Strasse 187, 47574 Goch, Germany, P.O. Box 20 21 20, 47568 Goch, Germany, T. +49 2823 9288 770, F. +49 2823 9288 7799



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## Inhalation grade Lactose (EU)

Product group: Inhalation

Brand name: Respitose®

Product description: Lactose Monohydrate
Lactose Anhydrous



*Table 2: Results of elemental impurities in Respitose® produced in Veghel, The Netherlands*

| Metal | Batch Limit (ppm) | Batch Report limit (ppm) | Respitose® 107NPPN (ppm) | Respitose® 109WNMS (ppm) | Respitose® 10BXK1M (ppm) |
|---|---|---|---|---|---|
| Cadmium | 0.3 | 0.005 | <0.005 | <0.005 | <0.005 |
| Lead | 0.5 | 0.01 | <0.01 | <0.01 | <0.01 |
| Arsenic | 0.2 | 0.005 | <0.010* | <0.005 | <0.005 |
| Mercury | 0.1 | 0.006 | <0.006 | <0.006 | <0.006 |
| Cobalt | 0.3 | 0.005 | <0.005 | <0.005 | <0.005 |
| Vanadium | 0.1 | 0.002 | <0.002 | 0.006 | <0.002 |
| Nickel | 0.6 | 0.030 | 0.074 | <0.03 | <0.03 |
| Selenium | 13 | 0.004 | <0.004 | <0.004 | <0.004 |
| Lithium | 2.5 | 0.004 | <0.004 | <0.004 | <0.004 |
| Antimony | 2 | 0.005 | <0.005 | <0.005 | <0.005 |
| Barium | 30 | 0.005 | 0.025 | 0.015 | 0.010 |
| Molybdenum | 1 | 0.020 | 0.041 | 0.046 | 0.038 |
| Copper | 3 | 0.010 | <0.010 | <0.010 | <0.010 |
| Tin | 6 | 0.25 | <0.010* | <0.010* | <0.25 |
| Chromium | 0.3 | 0.030 | <0.03 | <0.03 | <0.03 |
| Aluminium | None | 0.200 | 0.51 | 0.84 | 0.45 |
| Strontium | None | 0.005 | 0.027 | 0.020 | 0.016 |

*At time of measurement the reporting limit was different

A risk assessment was performed. This document and raw data are available for review during audits. Conclusion of the risk assessment is that all values obtained are below 30% of the limits and thus do not need additional control, the change control procedure is the key to maintain this situation. The levels of ICH Q3D (R2) relevant elemental impurities are monitored on regular basis.

This statement substitutes all previous versions issued for the brand names mentioned above.
We trust this information, which is made up to the best of our knowledge, will be helpful to you.

With kindest regards,

**Name** : Peter Ebben
**Job title** : Global Quality Control Manager
**Signature** :

This document is controlled by a validated, electronic system and is valid without signature.
The above facsimile signature is only for display.

DFE Pharma GmbH & Co. KG
Klever Strasse 187, 47574 Goch, Germany, P.O. Box 20 21 20, 47568 Goch, Germany, T. +49 2823 9288 770, F. +49 2823 9288 7799