

**Reliability assessment of selected references used for carcinogenic potency
comparison of Zirconia Aluminosilicate Refractory Ceramic Fibres and
Aluminosilicate Refractory Ceramic Fibres with Crocidolite**

Contractor:

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On behalf of:

**Austrian Association for Building Materials &
Ceramic Industries**

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1 Introduction

Zirconia Aluminosilicate Refractory Ceramic Fibres and Aluminosilicate Refractory Ceramic Fibres also described as aluminosilicate wools (according EN 1094-1: 2008) were recently included in the REACH candidate list with far reaching consequences for the respective industry. Since the classification of the above mentioned fibers as carcinogen category 2 according to directive 67/548/EEC (Category 1B according to the criteria of the CLP regulation, EC (No) 1272/2008) in 1997 a considerable number of new data and reviews has been published. Open questions with regard to the definition of substance identity and with regard to classification, including the evaluation of the newly generated data, prompted the respective industry to search for further steps to be taken for a scientific and regulatory re-evaluation and cooperation with regulators.

The Austrian Association for Building Materials & Ceramic Industries contracted the Umweltbundesamt GmbH for a proposal for a scientific re-evaluation of Zirconia Aluminosilicate Refractory Ceramic Fibres and Aluminosilicate Refractory Ceramic Fibres.

The Umweltbundesamt GmbH provided a comprehensive summary of the state of the discussion and recommended a transparent reevaluation which goes beyond standard requirements and should build the basis for an efficient multi-stakeholder discussion (Umweltbundesamt GmbH 2010)

As a follow up of this summary the Umweltbundesamt GmbH provides herewith a reliability assessment of the following references:

Pott, F., Roller, M., Rippe, R.M., Germann, P.G. and Bellmann, B. (1991): Tumours by the intraperitoneal and intrapleural routes and their significance for the classification of mineral fibres. In: Brown, R.C., Hoskins, J.A., Johnson, N.F. (eds): Mechanisms in fibre carcinogenesis (NATO ASI series 223.). New York, London: Plenum Press. pp. 547-565.

Pott, F., Roller, M., Ziem, U., Reiffer, F.J., Bellmann, B., Rosenbruch, R. and Huth, F. (1989): Carcinogenicity studies on natural and man-made fibres with the intraperitoneal test in rats. [Symposium Mineral fibres in the Non Occupational Environment. Lyon, 8.-10.9.1987]. In: Nonoccupational Exposure to Mineral Fibres. Ed. by J. Bignon, J. Peto and R. Saracci.- Lyon: International Agency for Research on Cancer. S. 173-179. (=IARC Scientific Publ. No. 90).

Pott, F., Ziem, U., Reiffer, F.J., Huth, F., Ernst, H. and Mohr, U. (1987): Carcinogenicity studies on fibres, metal compounds, and some other dusts in rats. Experimental Pathology, 32, 129-152.

Roller, M., Pott, F., Kamino, K., Althoff, G.H. and Bellmann, B. (1996): Results of current intraperitoneal carcinogenicity studies with mineral and vitreous fibres. Exp.Toxic.Pathol. 48, 3-12

The selection of these specific references from the ample literature on RCFs is only justified by the fact that these were considered as key references for carcinogenic potency comparisons of RCFs and Crocidolite in the recently submitted SVHC Dossier. This dossier suggests comparable carcinogenic potency of these two fiber types.

The reliability assessment provided in this report could be used as starting point for a transparent discussion and reevaluation of the carcinogenicity of RCFs. However, the evaluation of these 4 references is far from being a comprehensive evaluation of all available literature as recommended in the previous report (Umweltbundesamt GmbH 2010).

2 Results

The publications by Pott et al. (1989) and Pott et al. (1991) report data on RCFs tested in carcinogenicity studies using inter alia also intra-peritoneal administration of the test material. They appear to be of sufficient reliability in terms of test organism description, study design description, study results documentation and plausibility of study design and results. However, the test substance identification of the RCFs is not explicit in terms of mineral composition, which represents a relevant uncertainty if the results should be used to estimate carcinogenicity of the specific Aluminiumsilicate Wool and Zirconia Aluminosilicate Wool:

In Pott et al. (1989) results are presented from Ceramic Wool (MAN) and Ceramic Wool (Fiberfrax). A reference is given (Bellmann et al 1987) that informs on the composition of Ceramic Wool Manville and Ceramic Wool A3. While it can be assumed that Ceramic Wool Manville corresponds to Ceramic Wool (MAN) it is not explicitly clear whether Ceramic Wool A3 is identical to Fiberfrax. However MAN and A3 represent fibers with Al₂O₃ contents of about 47% and SiO₂ contents of about 52%.

In Pott et al. (1991) results are presented from Al-Silicates Fiberfrax I, Fiberfrax II and Manville 5. No information and no reference is given for the composition of these Al-Silicates. Especially the composition of the fiber "Fiberfrax I" would be an important information for the comparative assessment of Fiberfrax I and Crocidolite, since just Fiberfrax I showed median fiber dimensions comparable to the Crocidolite sample.

In both publications for RCF evaluation (Pott et al. 1989, Pott et al. 1991) there is some minor uncertainty about the percentage of WHO fibers longer than 20 µm which is a critical determinant for potency estimates:

In Pott et al. (1989) a median length of fiber (with aspect ratio 5:1, L>5, D<3 µm) is given as 16 µm (MAN) or 13 µm (Fiberfrax), which means that about 50% of these fibers may be longer than 20 µm, but no more precise information is provided.

In Pott et al. (1991) a median of fiber length (with aspect ratio of 5:1, L>5, D<2) is given as 13 to 16 µm for Fiberfrax II and Manville5, which means that roughly about 50% of these fibers may be longer than 20 µm. For Fiberfrax I a median fiber length is given as 5.5 µm, which means that probably a very low percentage is longer than 20 µm, but no more precise information is provided.

The two references for carcinogenic potency estimates of Crocidolite (Pott et al. 1987, Roller et al. 1996) appear to be of sufficient overall reliability when the information on fiber number and fiber definition for the study by Pott et al. (1987) provided by personal communication between Dr. Roller and author of SVHC dossier is taken into consideration:

There remains some overall minor uncertainty about the content of WHO fibers longer than 20 µm in the study by Pott et al. (1987). The publication indicates only the median for fiber length (2.1 µm) and diameter (0.2µm) but further information on fiber dimensions can be taken from the cited reference Muhle et al. (1986): fiber length: 10%< 0.9, 50%< 2.1, 90% < 7.7 µm; fiber diameter: 10%< 0.09, 50% < 0.20, 90% < 0.36µm. As already mentioned the fiber definition (aspect ratio 5:1, L>5, D<2) is only available from personal communication between Dr. Roller and the author of the SVHC dossier. Furthermore there is some uncertainty about percentage of fibers longer than 20 µm: 50% of fibers shorter than 2.1 µm and 90% of fibers shorter than 7.7 µm indicate that just a very low percentage of fibers with L>20 µm may be present, but no more precise information is provided.

However, in [Roller et al. 1996](#) it is explicitly stated that 15% of WHO fibers were longer than 20 µm.

For a comparative potency estimate the RCF Fiberfrax I is most important since it contains the shorter fiber length (median 5.5 µm) that is better comparable to the Crocidolite samples (median 2.1 µm and 1.4 µm). As summarized above the mineral composition of Fiberfrax I is not explicit or traceable from the publication (Pott et al. 1991) and there is some minor uncertainty with regard to long fiber content in Fiberfrax I and the Crocidolite samples.

The analytical method of fiber dose is not detailed in any of the 4 publications, but more information can be traced in the references given therein, except for the Pott et al (1987) reference for Crocidolite.

Information on feeding, housing and SPF conditions are scarce in all four references and related citations.

For a detailed evaluation of all 4 studies using the ToxRTool please see the Annex III to this report.

The general methodical uncertainties of results from rat intra-peritoneal studies for human toxicology are discussed in chapter 2 and 4.3. of the earlier Umweltbundesamt GmbH (2010) report. In short, there are differences between rats and humans with regard to fiber deposition, consequent excretion/katabolic kinetics and related toxicodynamics. Intra-peritoneal experiments circumvent differences in deposition and kinetics and render the experiment independent from the overload effect (unspecific carcinogenicity from lung doses above Maximum Fiber Tolerated Dose, MFTD). Clearly the deposition and kinetics play a key role in fiber carcinogenicity but the difficulties and uncertainties to model them appropriately is used as an argument to support properly conducted intra-peritoneal studies as more reliable for comparative fiber hazard estimates.

There may also be uncertainty if the dose is above the local peritoneal maximum tolerated dose (MTD), but in the references analyzed here the fiber doses were all below 10^9 fibers which is the recommended dose according to Bernstein et Riego-Sintes (1999).

No attempt was undertaken to review other available literature on RCFs in order to exclude that other confirmatory or contradictory data are available for comparative assessment of RCFs with asbestos.

3 Conclusion

Restriction of reliability of the reviewed data (Pott et al 1989, Pott et al. 1991, Pott et al 1987, Roller et al. 1996) originates predominantly from uncertainty with regard to mineral identity of Fiberfrax and Manville and with regard to the fiber size distribution as well as limited traceability of fiber analytics and feeding/housing/SPF conditions within the experiments.

In summary the RCF data in Pott et al 1989, Pott et al. 1991 as well as the Crocidolite data in Pott et al 1987 were attributed with a Klimisch score of 3, and the Crocidolite data in Roller et al. 1996 were attributed with a Klimisch score of 1.

This means the RCF data and the Crocidolite data from these Pott studies should generally not be used as key study data, but may still be useful in weight-of-evidence approaches or as supportive information. The suitability of these RCF and Crocidolite data for potency comparison is very low, if a conclusion is intended specific for strictly defined aluminum silicate RCFs. However, if the intention is to estimate potencies of amorphous aluminum silicate RCFs in general for comparison with Crocidolite these Pott data may still be considered useful within a total weight of evidence approach.

Other general methodical uncertainties of results from rat intra-peritoneal studies for human toxicity estimates need to be acknowledged (Umweltbundesamt GmbH 2010).

Without having carried out a detailed review of all available data on RCFs we are not in the position to provide a comprehensive conclusion on the respective hazard estimate.

The need for the application of the precautionary principle (COM 2000) has to be respected as a standard requirement for all hazard and risk assessments. It is most relevant in case of increased methods and results uncertainty and high potential health or environmental impact.

4 Declaration of interest

This project was financed by the Austrian Association for Building Materials & Ceramic Industries. The authors confirm that a fully independent scientific assessment was elaborated.

Annex 1: Reference list

Annex 2: List of abbreviations

Annex 3: ToxRTool

Annex 1 – Reference List

Bellmann B, Muhle H, Pott F, König H, Klöppel H, Spurny K 1987. Persistence of man-made mineral fibres (MMMF) and asbestos in rat lungs. *Ann Occup Hyg.* 31(4B), 693-709.

Bernstein D.M. et Riego-Sintes, J.M. 1999. Methods for the Determination of the Hazardous Properties for Human Health of Man Made Mineral Fibres (MMMF) (Report No. EUR 18748), Brussels, European Commission Joint Research Centre, European Chemicals Bureau.

COM 2000. Communication from the commission on the precautionary principle. Brussels, 02.02.2000, COM(2000) 1

Muhle H, Pott F, Bellmann B, Takenaka S, Ziem U 1987. Inhalation and injection experiments in rats to test the carcinogenicity of MMMF. *Ann Occup Hyg.* 31(4B), 755-64.

Pott F. 1987. Problems in defining carcinogenic fibres. *Ann Occup Hyg.*;31(4B), 799-802.

Pott, F., Roller, M., Althoff, G.H., Kamino, K., Bellmann, B. und Ulm, K. 1993. Beurteilung der Kanzerogenität inhalierbarer Fasern. In: *Faserförmige Stäube. Vorschriften, Wirkungen, Messungen, Minderung.* Kolloquium Fulda, 6.-9. September 1993. VDI-Verlag, Düsseldorf, S. 17-79, 1993. (VDI-Berichte 1075).

Pott, F., Roller, M., Rippe, R.M., Germann, P.G. and Bellmann, B. 1991. Tumours by the intraperitoneal and intrapleural routes and their significance for the classification of mineral fibres. In: Brown, R.C., Hoskins, J.A., Johnson, N.F. (eds): *Mechanisms in fibre carcinogenesis (NATO ASI series 223.)*. New York, London: Plenum Press. pp. 547-565.

Pott, F., Roller, M., Ziem, U., Reiffer, F.J., Bellmann, B., Rosenbruch, R. and Huth, F. 1989. Carcinogenicity studies on natural and man-made fibres with the intraperitoneal test in rats. [Symposium Mineral fibres in the Non Occupational Environment. Lyon, 8.-10.9.1987]. In: *Nonoccupational Exposure to Mineral Fibres.* Ed. by J. Bignon, J. Peto and R. Saracci.- Lyon: International Agency for Research on Cancer. S. 173-179. (=IARC Scientific Publ. No. 90).

Pott, F., Ziem, U., Reiffer, F.J., Huth, F., Ernst, H. and Mohr, U. 1987. Carcinogenicity studies on fibres, metal compounds, and some other dusts in rats. *Experimental Pathology*, 32, 129-152.

Roller, M., Pott, F., Kamino, K., Althoff, G.H. and Bellmann, B. 1996. Results of current intraperitoneal carcinogenicity studies with mineral and vitreous fibres. *Exp.Toxic.Pathol.* 48, 3-12

Umweltbundesamt GmbH 2010. Proposal for a scientific re-evaluation of Zirconia Aluminosilicate Refractory Ceramic Fibres and Aluminosilicate Refractory Ceramic Fibres. FINAL REPORT, 2010-07-02.

Annex 2 - List of Abbreviations

AES	Alkaline Earth Silicate Wools
ATSDR	Agency for Toxic Substances and Disease Registry
CLP	EU regulation on Classification, Labelling and Packaging of substances and mixtures
GHS	Globally Harmonized System of Classification and Labelling of Chemicals
GMD	Geometric Mean Diameter
HTIW	High Temperature Insulation Wool
IARC	International Agency for Research on Cancer
IOM	Institute of Occupational Medicine
IUPAC	International Union of Pure and Applied Chemistry
JRC	Joint Research Center
MFTD	Maximum Fiber Tolerated Dose
MMMMF	Man-Made Mineral Fibers
MMVF	Man-Made Vitreous Fibers
NIOSH	The National Institute for Occupational Safety and Health
NTP	National Toxicology Program
PCW	Polycrystalline Wools
RCF/ASW	Refractory Ceramic Fibers / Aluminosilicate Wools
UVCB	Substances of Unknown or Variable composition, Complex reaction products or Biological Materials

Annex 3 - ToxRTool – Results

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Explanations to ToxRTool

Objective: ToxRTool is designed to assess the inherent quality, also called reliability, of toxicological data as reported in a publication or a test report.

This tool essentially comprises a list of evaluation criteria. Criteria are subdivided in five groups:

I: Test substance identification, II: Test system characterisation, III: Study design description,

Per criterion either one ('1') or no ('0') point can be assigned. If a criterion is met, assign '1', if not assign '0'. Please choose from the respective drop-down list.

In total 21 points for in vivo studies, 18 points for in vitro studies can be assigned. A reliability categorisation based on the total number of points is given below.

Criteria written in red have special importance: points for each of the red criteria are necessary to achieve Reliability category 1 or 2. **Please evaluate with special care!**

Data entry is requested in (and is also restricted to) the fields shaded in green.

Reliability categorisation (definition of categories according to Klimisch et al. 1997)

(Proposed) consequence

	in vivo	in vitro		
1	18-21	15-18	reliable without restrictions	useful, check relevance for intended purpose
2	13-17	11-14	reliable with restrictions	potentially useful, check relevance for intended purpose
3	<13 or not all red criteria met	<11 or not all red criteria met	not reliable	generally not to be used as key study, but depending on the shortcomings of the study it may still be useful in weight-of-evidence approaches or as supportive information
4			not assignable: documentation insufficient (reviews, handbooks, other secondary sources)	generally not to be used as key study, but depending on the shortcomings of the study it may still be useful in weight-of-evidence approaches or as supportive information. (This category is not an outcome of this evaluation tool!)

In addition to the criteria for assessing data reliability, at the bottom of the worksheets there are some questions to be answered optionally ("Optional documentation of observations with importance to relevance"). These questions allow to document observations in a non-formalised way, which may be of importance for the further use of the information for regulatory or other purposes.

Reliability assessment of in vivo toxicity studies		
Study under evaluation		
Authors:		
Pott F., Roller M., Ziem U., Reiffer F.J., Bellmann B., Rosenbruch M., Huth F.		
Titel:		
Carcinogenicity studies on natural and man-made fibres with the intraperitoneal test in rats		
Testing facility, year, sponsor, study no. or bibliographic reference:		
Bignon J., Peto J., Saracci R. (ed). Non-Occupational exposure to mineral fibres, International Agency for Research on Cancer, Lyon, IARC Sci. Publ. No. 90, pp. 173-179 (1989)		
Explanations are available for most criteria and show up, when the cursor is moved over the criteria field. Please read carefully!		
Red criteria: the maximum score is needed for these criteria to achieve reliability category 1 or 2 (see worksheet Explanations): Please evaluate with special care!		
Criteria		Evaluator's explanations, comments on criteria, etc.
No.	Criteria Group I: Test substance identification	Score
1	Was the test substance identified?	0
2	Is the purity of the substance given?	0
3	Is information on the source/origin of the substance given?	0
4	Is all information on the nature and/or physico-chemical properties of the test item given, which you deem indispensable for judging the data (see explanation for examples)?	0
		0
Criteria Group II: Test organism characterisation		
5	Is the species given?	1
6	Is the sex of the test organism given?	1
7	Is information given on the strain of test animals plus, if considered necessary to judge the study, other specifications (see explanation for examples)?	0
8	Is age or body weight of the test organisms at the start of the study given?	1
9	For repeated dose toxicity studies only (give point for other study types): Is information given on the housing or feeding conditions?	0
		3
Criteria Group III: Study design description		
10	Is the administration route given?	1
11	Are doses administered or concentrations in application media given?	1
12	Are frequency and duration of exposure as well as time-points of observations explained?	1
13	Were negative (where required) and positive controls (where required) included (give point also, when absent but not required, see explanations for study types and their respective requirements on controls)?	1

14	Is the number of animals (in case of experimental human studies: number of test persons) per group given?	1	in table 2
15	Are sufficient details of the administration scheme given to judge the study (see explanation for examples)?	1	
16	For inhalation studies and repeated dose toxicity studies only (give point for other study types): Were achieved concentrations analytically verified or was stability of the test substance otherwise ensured or made plausible?	1	method of fibre measurement not explicit; more detailed information traceable in reference given (Bellmann et al. 1987)
		7	
	Criteria Group IV: Study results documentation		
17	Are the study endpoint(s) and their method(s) of determination clearly described?	1	just tumor induction: parts of tumors or organs with macroscopically suspected tumor tissue were fixed in formalin and prepared for histological examination on paraffin-embedded H&E stained sections. Furthermore tumor adhesion and life-span was measured.
18	Is the description of the study results for all endpoints investigated transparent and complete?	1	
19	Are the statistical methods applied for data analysis given and applied in a transparent manner (give also point, if not necessary/applicable, see explanations)?	1	no statistical methods used, but considered to be dispensable
		3	
	Criteria Group V: Plausibility of study design and results		
20	Is the study design chosen appropriate for obtaining the substance-specific data aimed at (see explanations for details)?	1	for summary of uncertainties of results from intraperitoneal studies see chapter 4.3 of Umweltbundesamt 2010.
21	Are the quantitative study results reliable (see explanations for arguments)?	1	
		2	
		15	
	A Numerical result leads to initial Category:	2	
	B Checking red scores leads to revised Category:	3	
	C Evaluator's proposal: Category:		
	D Justification in case evaluator deviates from B:		
	Optional documentation of observations with importance to relevance		
	During the course of the quality assessment observations may be made which are important for discussing the relevance of the data for specific purposes. The optional possibility is provided here to document these observations for future use.		
	What is the purpose of this quality evaluation (data documentation for use under REACH, classification activity under GHS, ECVAM validation activities, other)?		
	estimation of carcinogenic potency of RCF compared to asbestos		
	Study conducted according to recent OECD or EU guidelines (or other, e.g. national guidelines)? If yes, which ones? Study conducted under GLP conditions?		
	referene to guideline /GLP /SPF conditions not explicit		
	(If not a guideline study): Does a guideline exist for the study endpoint(s) under investigation?		
	1999. Bernstein D.M., Riego Sintes J.M. JRC. EUR 18748 EN. Methods for the Determinatino of the Hazardous Properties for Human Health of MMMF.		

	Are you aware of relevant deviations from the guideline(s) in the study evaluated? If yes, which one?		
	no details about sample preparation and application and histo/pathological evaluation are given, but no specific concern is evident		
	Did you make observations with importance to the regulatory use of the data (example 1: evaluator may hint that a whole body inhalation study was performed with a substance, for which profound percutaneous absorption is expected or known, leading to substantial percutaneous uptake in addition to inhalation uptake; example 2: an Ames reversion assay was performed with strains able to identify frame-shift mutations only or without external metabolic activation; example 3: evaluator is in possession of positive evidence that the results obtained with the in vitro study under evaluation, in conjunction with known toxicokinetic data, are useful to assess the nephrotoxicity of the substance in humans)?		
	Would you like to make other/general comments on the usability of the data?		
	for summary of uncertainties of results from intraperitoneal studies see chapters 2 and 4.3 of Umweltbundesamt 2010.		

Reliability assessment of in vivo toxicity studies		
Study under evaluation		
Authors:		
	Pott F., Roller M., Rippe R.M., Germann P.G., Bellmann B.	
Titel:		
	Tumours by the intraperitoneal and intrapleural routes and their significance for the classification of mineral fibres.	
Testing facility, year, sponsor, study no. or bibliographic reference:		
	Mechanisms in Fibre Carcinogenesis, edited by R.C. Brown et al., Plenum Press, New York 1991	
Explanations are available for most criteria and show up, when the cursor is moved over the criteria field. Please read carefully!		
Red criteria: the maximum score is needed for these criteria to achieve reliability category 1 or 2 (see worksheet Explanations): Please evaluate with special care!		
Criteria		Evaluator's explanations, comments on criteria, etc.
No.	Criteria Group I: Test substance identification	Score
1	Was the test substance identified?	0
2	Is the purity of the substance given?	0
3	Is information on the source/origin of the substance given?	0
4	Is all information on the nature and/or physico-chemical properties of the test item given, which you deem indispensable for judging the data (see explanation for examples)?	0
		0
Criteria Group II: Test organism characterisation		
5	Is the species given?	1
6	Is the sex of the test organism given?	1
7	Is information given on the strain of test animals plus, if considered necessary to judge the study, other specifications (see explanation for examples)?	0
8	Is age or body weight of the test organisms at the start of the study given?	0
9	For repeated dose toxicity studies only (give point for other study types): Is information given on the housing or feeding conditions?	0
		2
Criteria Group III: Study design description		
10	Is the administration route given?	1
11	Are doses administered or concentrations in application media given?	1
12	Are frequency and duration of exposure as well as time-points of observations explained?	1
13	Were negative (where required) and positive controls (where required) included (give point also, when absent but not required, see explanations for study types and their respective requirements on controls)?	1
14	Is the number of animals (in case of experimental human studies: number of test persons) per group given?	1

15	Are sufficient details of the administration scheme given to judge the study (see explanation for examples)?	0	no information on dose preparation and concentration and volume applied
16	For inhalation studies and repeated dose toxicity studies only (give point for other study types): Were achieved concentrations analytically verified or was stability of the test substance otherwise ensured or made plausible?	1	all measurements by SEM, more detailed information traceable in reference given (Bellmann et al. 1987)
		6	
	Criteria Group IV: Study results documentation		
17	Are the study endpoint(s) and their method(s) of determination clearly described?	1	number of animals with tumors, lifespan
18	Is the description of the study results for all endpoints investigated transparent and complete?	0	it is explicit that number of animals with (uterus) tumors not related to fiber exposure were not taken into account, but not explicit what the number/proportion of these not accountable tumors was
19	Are the statistical methods applied for data analysis given and applied in a transparent manner (give also point, if not necessary/applicable, see explanations)?	1	no statistical methods used, but considered to be dispensable
		2	
	Criteria Group V: Plausibility of study design and results		
20	Is the study design chosen appropriate for obtaining the substance-specific data aimed at (see explanations for details)?	1	for summary n of uncertainties of results from intraperitoneal studies see chapter 4.3 of Umweltbundesamt 2010.
21	Are the quantitative study results reliable (see explanations for arguments)?	1	
		2	
		12	
	A Numerical result leads to initial Category:	3	
	B Checking red scores leads to revised Category:	3	
	C Evaluator's proposal: Category:		
	D Justification in case evaluator deviates from B:		
	Optional documentation of observations with importance to relevance		
	During the course of the quality assessment observations may be made which are important for discussing the relevance of the data for specific purposes. The optional possibility is provided here to document these observations for future use.		
	What is the purpose of this quality evaluation (data documentation for use under REACH, classification activity under GHS, ECVAM validation activities, other)?		
	estimation of carcinogenic potency of RCF compared to asbestos		
	Study conducted according to recent OECD or EU guidelines (or other, e.g. national guidelines)? If yes, which ones? Study conducted under GLP conditions?		
	referene to guideline /GLP conditions not explicit, not explicit if SPF conditions were applied		
	(If not a guideline study): Does a guideline exist for the study endpoint(s) under investigation?		

	1999. Bernstein D.M., Riego Sintes J.M. JRC. EUR 18748 EN. Methods for the Determination of the Hazardous Properties for Human Health of MMMF.		
	Are you aware of relevant deviations from the guideline(s) in the study evaluated? If yes, which one?		
	no details about sample preparation and histo/pathological evaluation are given, but no specific concern is evident		
	Did you make observations with importance to the regulatory use of the data (example 1: evaluator may hint that a whole body inhalation study was performed with a substance, for which profound percutaneous absorption is expected or known, leading to substantial percutaneous uptake in addition to inhalation uptake; example 2: an Ames reversion assay was performed with strains able to identify frame-shift mutations only or without external metabolic activation; example 3: evaluator is in possession of positive evidence that the results obtained with the in vitro study under evaluation, in conjunction with known toxicokinetic data, are useful to assess the nephrotoxicity of the substance in humans)?		
	Would you like to make other/general comments on the usability of the data?		
	footnotes of the results table 4 seem to be confused with the footnotes of table 3, leading to some uncertainty with regard to dosing scheme (injections with weekly interval?) and reference for fiber size analytics. For summary of uncertainties of results from intraperitoneal studies see chapters 2 and 4.3 of Umweltbundesamt 2010.		

Reliability assessment of in vivo toxicity studies		
Study under evaluation		
Authors:		
Pott F., Ziem U., Reiffer F.J., Huth F., Ernst H., Mohr U.		
Titel:		
Carcinogenicity studies on fibres, metal compounds and some other dusts in rats		
Testing facility, year, sponsor, study no. or bibliographic reference:		
Exp. Pathol. 32, p 129-152 (1987)		
Explanations are available for most criteria and show up, when the cursor is moved over the criteria field. Please read carefully!		
Red criteria: the maximum score is needed for these criteria to achieve reliability category 1 or 2 (see worksheet Explanations): Please evaluate with special care!		
Criteria		Evaluator's explanations, comments on criteria, etc.
No.	Criteria Group I: Test substance identification	Score
1	Was the test substance identified?	0
2	Is the purity of the substance given?	0
3	Is information on the source/origin of the substance given?	1
4	Is all information on the nature and/or physico-chemical properties of the test item given, which you deem indispensable for judging the data (see explanation for examples)?	0
		1
Criteria Group II: Test organism characterisation		
5	Is the species given?	1
6	Is the sex of the test organism given?	1
7	Is information given on the strain of test animals plus, if considered necessary to judge the study, other specifications (see explanation for examples)?	1
8	Is age or body weight of the test organisms at the start of the study given?	0
9	For repeated dose toxicity studies only (give point for other study types): Is information given on the housing or feeding conditions?	0
		3
Criteria Group III: Study design description		
10	Is the administration route given?	1
11	Are doses administered or concentrations in application media given?	0
12	Are frequency and duration of exposure as well as time-points of observations explained?	1

13	Were negative (where required) and positive controls (where required) included (give point also, when absent but not required, see explanations for study types and their respective requirements on controls)?	1	saline as negative control
14	Is the number of animals (in case of experimental human studies: number of test persons) per group given?	1	64 rats
15	Are sufficient details of the administration scheme given to judge the study (see explanation for examples)?	1	
16	For inhalation studies and repeated dose toxicity studies only (give point for other study types): Were achieved concentrations analytically verified or was stability of the test substance otherwise ensured or made plausible?	0	method of fibre measurement not explicit, reference given (Muhle et al. 1986: SEM analysis), but no methodical details.
		5	
	Criteria Group IV: Study results documentation		
17	Are the study endpoint(s) and their method(s) of determination clearly described?	1	number of animals with tumors, life span
18	Is the description of the study results for all endpoints investigated transparent and complete?	0	it is explicit that number of animals with (uterus) tumors not related to fiber exposure were not taken into account, but not explicit what the number/proportion of these not accountable tumors was
19	Are the statistical methods applied for data analysis given and applied in a transparent manner (give also point, if not necessary/applicable, see explanations)?	1	no statistical methods used, but considered to be dispensable
		2	
	Criteria Group V: Plausibility of study design and results		
20	Is the study design chosen appropriate for obtaining the substance-specific data aimed at (see explanations for details)?	1	for summary of uncertainties of results from intraperitoneal studies see chapter 4.3 of Umweltbundesamt 2010.
21	Are the quantitative study results reliable (see explanations for arguments)?	1	
		2	
		13	
	A Numerical result leads to initial Category:	2	
	B Checking red scores leads to revised Category:	3	
	C Evaluator's proposal: Category:		
	D Justification in case evaluator deviates from B:		
	Optional documentation of observations with importance to relevance		
	During the course of the quality assessment observations may be made which are important for discussing the relevance of the data for specific purposes. The optional possibility is provided here to document these observations for future use.		
	What is the purpose of this quality evaluation (data documentation for use under REACH, classification activity under GHS, ECVAM validation activities, other)?		
	estimation of carcinogenic potency of RCF compared to asbestos		
	Study conducted according to recent OECD or EU guidelines (or other, e.g. national guidelines)? If yes, which ones? Study conducted under GLP conditions?		
	referene to guideline /GLP conditions not explicit, conventional (rather than SPF) conditions explicit		

	(If not a guideline study): Does a guideline exist for the study endpoint(s) under investigation?		
	1999. Bernstein D.M., Riego Sintes J.M. JRC. EUR 18748 EN. Methods for the Determination of the Hazardous Properties for Human Health of MMMF.		
	Are you aware of relevant deviations from the guideline(s) in the study evaluated? If yes, which one?		
	no details about histo/pathological evaluation are given, but no specific concern is evident		
	Did you make observations with importance to the regulatory use of the data (example 1: evaluator may hint that a whole body inhalation study was performed with a substance, for which profound percutaneous absorption is expected or known, leading to substantial percutaneous uptake in addition to inhalation uptake; example 2: an Ames reversion assay was performed with strains able to identify frame-shift mutations only or without external metabolic activation; example 3: evaluator is in possession of positive evidence that the results obtained with the in vitro study under evaluation, in conjunction with known toxicokinetic data, are useful to assess the nephrotoxicity of the substance in humans)?		
	Would you like to make other/general comments on the usability of the data?		
	for summary of uncertainties of results from intraperitoneal studies see chapters 2 and 4.3 of Umweltbundesamt 2010.		

Reliability assessment of in vivo toxicity studies		
Study under evaluation		
Authors:		
	Roller M., Pott F., Kamino K., Althoff G.H., Bellmann B.	
Titel:		
	Results of current intraperitoneal carcinogenicity studies with mineral and vitreous fibres	
Testing facility, year, sponsor, study no. or bibliographic reference:		
	Exp. Toxic Pathol 48, p 3-12 (1996)	
Explanations are available for most criteria and show up, when the cursor is moved over the criteria field. Please read carefully!		
Red criteria: the maximum score is needed for these criteria to achieve reliability category 1 or 2 (see worksheet Explanations): Please evaluate with special care!		
Criteria		Evaluator's explanations, comments on criteria, etc.
No.	Criteria Group I: Test substance identification	Score
1	Was the test substance identified?	1
2	Is the purity of the substance given?	1
3	Is information on the source/origin of the substance given?	0
4	Is all information on the nature and/or physico-chemical properties of the test item given, which you deem indispensable for judging the data (see explanation for examples)?	1
		3
Criteria Group II: Test organism characterisation		
5	Is the species given?	1
6	Is the sex of the test organism given?	1
7	Is information given on the strain of test animals plus, if considered necessary to judge the study, other specifications (see explanation for examples)?	0
8	Is age or body weight of the test organisms at the start of the study given?	1
9	For repeated dose toxicity studies only (give point for other study types): Is information given on the housing or feeding conditions?	0
		3
Criteria Group III: Study design description		
10	Is the administration route given?	1
11	Are doses administered or concentrations in application media given?	1
12	Are frequency and duration of exposure as well as time-points of observations explained?	1
13	Were negative (where required) and positive controls (where required) included (give point also, when absent but not required, see explanations for study types and their respective requirements on controls)?	1
14	Is the number of animals (in case of experimental human studies: number of test persons) per group given?	1
15	Are sufficient details of the administration scheme given to judge the study (see explanation for examples)?	1
16	For inhalation studies and repeated dose toxicity studies only (give point for other study types): Were achieved concentrations analytically verified or was stability of the test substance otherwise ensured or made plausible?	1

		7	
	Criteria Group IV: Study results documentation		
17	Are the study endpoint(s) and their method(s) of determination clearly described?	1	mesothelioma macroscopically and histopath., bw., cumulative mortality, survival time, tumor types not considered fiber induced (uterus,..)
18	Is the description of the study results for all endpoints investigated transparent and complete?	1	sufficiently
19	Are the statistical methods applied for data analysis given and applied in a transparent manner (give also point, if not necessary/applicable, see explanations)?	1	no statistical methods used, but considered to be dispensable
		3	
	Criteria Group V: Plausibility of study design and results		
20	Is the study design chosen appropriate for obtaining the substance-specific data aimed at (see explanations for details)?	1	summary of uncertainties of results from intraperitoneal studies see chapter 4.3 of Umweltbundesamt 2010.
21	Are the quantitative study results reliable (see explanations for arguments)?	1	
		2	
		18	
	A Numerical result leads to initial Category:	1	
	B Checking red scores leads to revised Category:	1	
	C Evaluator's proposal: Category:		
	D Justification in case evaluator deviates from B:		
	Optional documentation of observations with importance to relevance		
	During the course of the quality assessment observations may be made which are important for discussing the relevance of the data for specific purposes. The optional possibility is provided here to document these observations for future use.		
	What is the purpose of this quality evaluation (data documentation for use under REACH, classification activity under GHS, ECVAM validation activities, other)?		
	estimation of carcinogenic potency of RCF compared to asbestos		
	Study conducted according to recent OECD or EU guidelines (or other, e.g. national guidelines)? If yes, which ones? Study conducted under GLP conditions?		
	referene to guideline /GLP /SPF conditions not explicit		
	(If not a guideline study): Does a guideline exist for the study endpoint(s) under investigation?		
	1999. Bernstein D.M., Riego Sintes J.M. JRC. EUR 18748 EN. Methods for the Determinatino of the Hazardous Properties for Human Health of MMMF.		
	Are you aware of relevant deviations from the guideline(s) in the study evaluated? If yes, which one?		
	no details about sample preparation and application and histo/pathological evaluation are given, but no specific concern is evident		

	<p>Did you make observations with importance to the regulatory use of the data (example 1: evaluator may hint that a whole body inhalation study was performed with a substance, for which profound percutaneous absorption is expected or known, leading to substantial percutaneous uptake in addition to inhalation uptake; example 2: an Ames reversion assay was performed with strains able to identify frame-shift mutations only or without external metabolic activation; example 3: evaluator is in possession of positive evidence that the results obtained with the in vitro study under evaluation, in conjunction with known toxicokinetic data, are useful to assess the nephrotoxicity of the substance in humans)?</p>		
	<p>Would you like to make other/general comments on the usability of the data?</p>		
	<p>summary of uncertainties of results from intraperitoneal studies see chapters 2 and 4.3 of Umweltbundesamt 2010.</p>		