Leibniz Research Alliance Nanosafety

Summary

Nanotechnologically produced materials and products are more than ever the focus of current material developments, as they promise solutions for important fields of technology. The safe application of these materials is central to their sustainable application. Due to the large number of material types, the understanding of the processes induced by nanomaterials and the prediction of these processes is still limited. Thus does the topic not only represent a scientific challenge, it is also highly relevant to society.

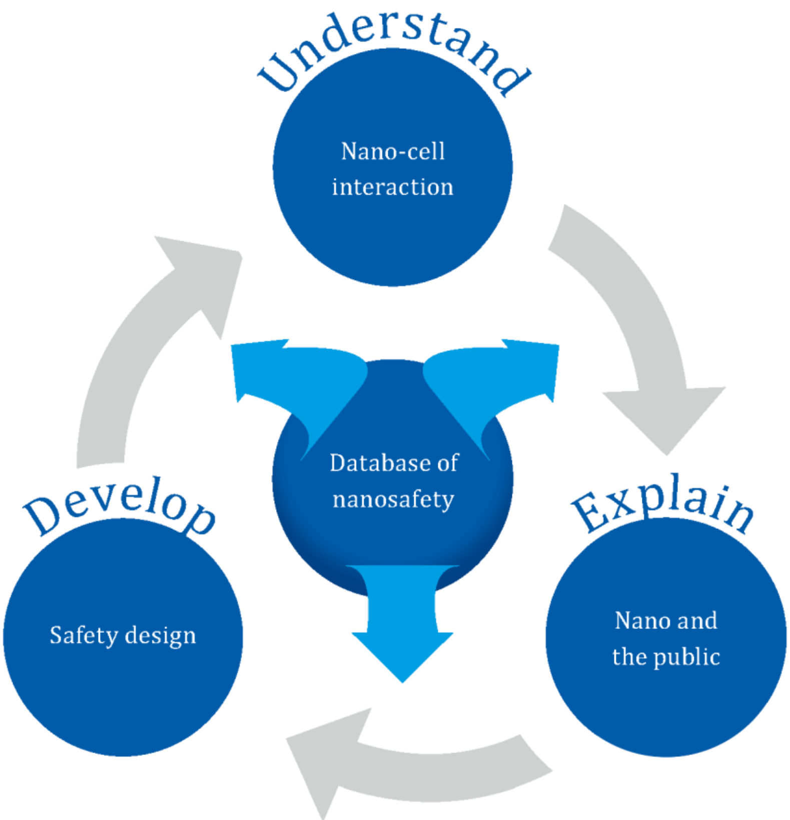

Figure 1: The central aims are to UNDERSTAND nanoparticle-induced effects, to DEVELOP safe nanomaterials and to EXPLAIN nano-related questions. Further, the partners of the alliance were working on establishing a RESEARCH DATA INFRASTRUCTURE that allows public access and subsequent use of our nanosafety data as the foundation for an improved and traceable risk assessment and regulation.

Within two funding periods, from 2012 to 20202, the Leibniz Research Alliance Nanosafety dealt with the safety of nanomaterials and nanoproducts. The focus was on four objectives (Fig. 1):

A Clarification of the mechanisms of action of nanomaterials and their effects on human health (Understand)
B Design of safe nanomaterials (Develop)
C Development of a digital infrastructure for nanosafety data (Research data infrastructure)
D Promotion of public discourse on nanosafety issues (Explain)

The four topics were addressed as part of collaborations between the partners involved and as part of national and international collaborations and projects. The results were published accordingly. Several ongoing projects and initiatives have an impact beyond the duration of the LRA, including the BMBF project NanoS-QM (2019-2021) and an application resulting from the network in the context of the national research data infrastructure.

The research activities led to intensive collaboration between the project partners and resulted in their increased integration and visibility within the national and international specialist community. The collaboration was further strengthened through the implementation of joint doctoral projects, studies and research stays at the partner institutes.

The partners of the LRA organised nationally and internationally visible events such as workshops and conferences. Articles in the (regional) press, radio and television reports, panel discussions and talks with politicians, as well as participation in events such as open days, Girls' Day, the BMBF student internship "Werkstoff-Ferien" helped to communicate the topic of nanosafety to a wide audience.

After 8 years (2 funding periods) of joint research on nanosafety, the members of the Leibniz Research Alliance Nanosafety decided to broaden the focus of their activities and transfer their expertise within the Leibniz Research Alliance Advanced Materials Safety on examination of safety and sustainability of advanced materials. To appropriately meet the challenges of the topic in breadth and depth, the number of involved partner institutes increased to 12.

Partners of the research alliance

An alliance of seven institutes that are devoted to materials science, cell biology, health and toxicology, immunology, occupational health and safety, scientific databases and knowledge communication work together towards a common goal.

INM	**INM - Leibniz Institute for New Materials, Saarbrücken** Nano Cell Interactions
ipf Leibniz-Institut für Polymerforschung Dresden	**Leibniz Institute for Polymer Research, Dresden** Functional nanostructured interfaces & polymer systems Biology-inspired interface and material design Functional nanocomposites and blends
IWT Leibniz-Institut für Werkstofforientierte Technologien	**Leibniz Institute for Materials Engineering IWT, Bremen** Process and Chemical Engineering

Nanosicherheit

IfADo	**Leibniz Research Centre for Working Environment and Human Factors, Dortmund** Toxicology
IWM Leibniz-Institut für Wissensmedien	**Leibniz Institute for Knowledge Media, Tübingen** Multimodal Interaction Lab
IUF Leibniz Research Institute for Environmental Medicine	**Leibniz Research Institute for Environmental Medicine, Düsseldorf** Environmentally-induced skin and lung ageing Particles, inflammation and genome integrity
FIZ Karlsruhe Leibniz-Institut für Informationsinfrastruktur	**FIZ-Karlsruhe - Leibniz Institute for Information Infrastructure**

Examples from our research

A Clarification of the mechanisms of action of nanomaterials and their effects on human health (Understand)

Interactions of nanomaterials with living organisms are decisive factors for the safety of these substances. The physicochemical properties of these materials may or may not impair the functions of the human body. The aim is to detect the interactions of nanomaterials with the human body and to analyse their mechanisms of action.

Respiration-like stretching of lung cells in cell culture model influences their reaction on nanoparticles

How do lung cells react on particles small enough to enter the deeper regions of the lung? Often, researchers investigate lung cells grown as culture models in the laboratory to answer this question. The results of those simplified models cannot be directly transferred to complex, living organisms. Researchers of the Leibniz Research Alliance Nanosafety, Saarland University and TU Dortmund analysed a cell culture model that mimics the real conditions a little closer – they grew human lung cells on flexible surfaces that were stretched in a respiration-like mode. Lung cells that were stretched reacted more strongly to added nanoparticles, in a way that resembled an inflammatory response.

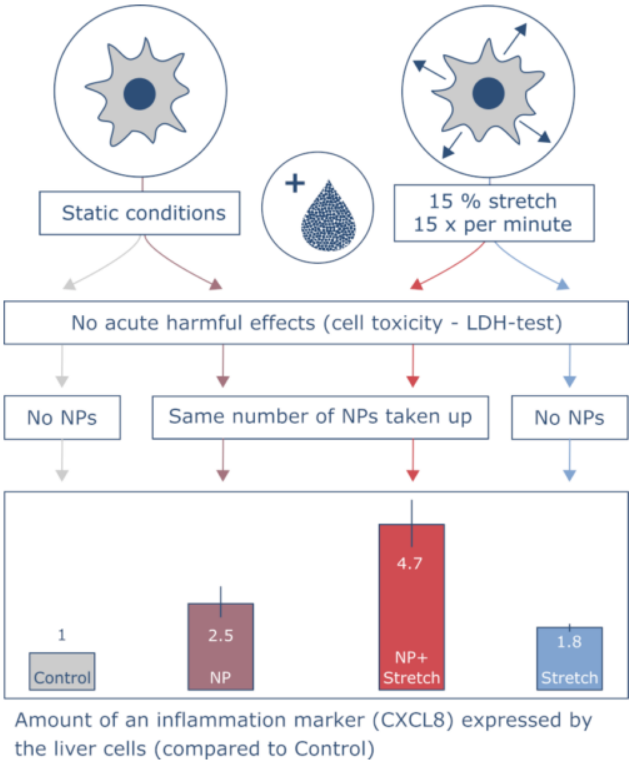

Figure 2: Illustration of the experimental conditions and testing methods of parts of the described study. The number of nanoparticles (NPs) were measured with fluorescence microscopy.

Funding: This study was partly financed by the Leibniz Research Alliance Nanosafety and the Leibniz Association.

Publication: Carmen Schmitz, Jennifer Welck, Isabella Tavernaro, Marianna Grinberg, Jörg Rahnenführer, Alexandra K. Kiemer, Christoph van Thriel, Jan G. Hengstler & Annette Kraegeloh, Mechanical strain mimicking breathing amplifies alterations in gene expression induced by SiO_2 NPs in lung epithelial cells. Nanotoxicology 13:9 (2019) 1227; https://doi.org/10.1080/17435390.2019.1650971

3D model of liver cells to improve safety evaluation of nanoparticles

With the aim of developing safer nanoparticles for biomedical applications, scientists of the group Nano-Cell Interactions at INM – Leibniz-Institute for New Materials and Pharmacelsus GmbH in Saarbrücken have studied a three-dimensional liver cell model. The model allows analysis of biomarkers in combination with information on penetration depth of the particles into the tissue. Therefore, it is better suited for nanoparticle testing and development than conventional two-dimensional cell models, where cells are growing as a single layer.

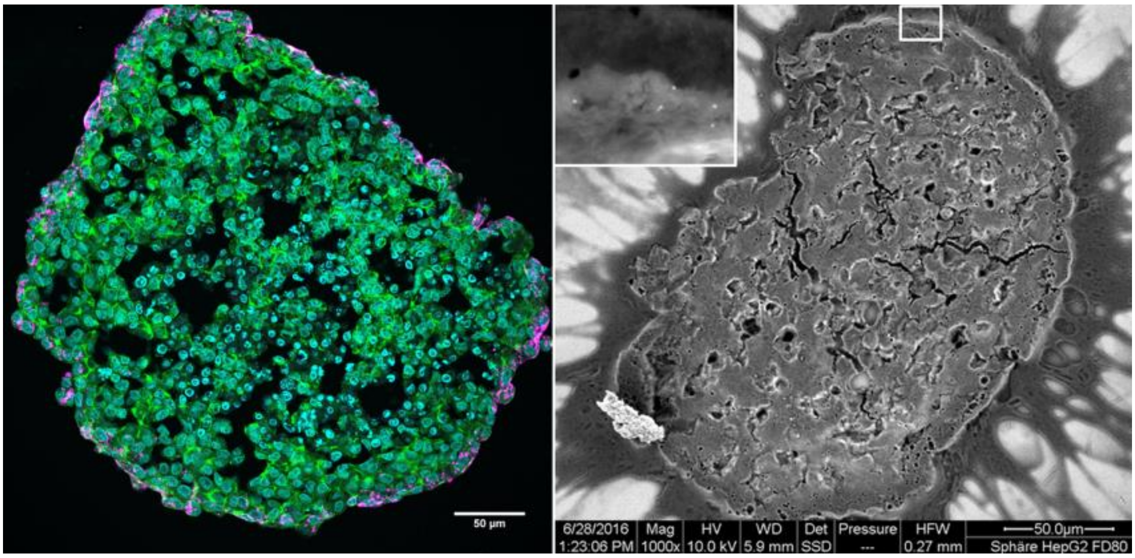

Figure 3: Left: Fluoreszence image of liver cell micro tissue (green: cytoskeleton, blue: nuclei) with silica nanoparticles (magenta) located at the border of the micro tissue.
Right: Elektron microscopy image of a liver cell drop. Individual nanoparticles are visible in the outer rim of the cell drop (white in detail on top left). [Jana Fleddermann]

Project: NanoDopa - Dopamin beladene Nanopartikel für therapeutische Zwecke

Duration: 2018 – 2021

Funding: The work was funded by the German Federal Ministry for Economic Affairs and Energy, in the framework of the Zentrale Innovationsprogramm Mittelstand (ZIM)-cooperation network NanoPharm in the project 'MORPHEUS'. The publication of this article was funded by the Open Access Fund of the Leibniz Association.

Publication: J. Fleddermann, J. Susewind, H. Peuschel, M. Koch, I. Tavernaro, A. Kraegeloh, Distribution of SiO2 nanoparticles in 3D liver microtissues. Int. J. Nanomed, 2019, 14, 1411-1431.
https://doi.org/10.2147/IJN.S189888

B Design of safe nanomaterials (Develop)

Knowledge of the interaction mechanisms between nanomaterials and biological systems is used to derive concepts that can be applied to the development of new materials. By the inclusion of Safety by Design concepts into material development, we aim to cater for current developments in industrial production, providing test systems for industrial applications.

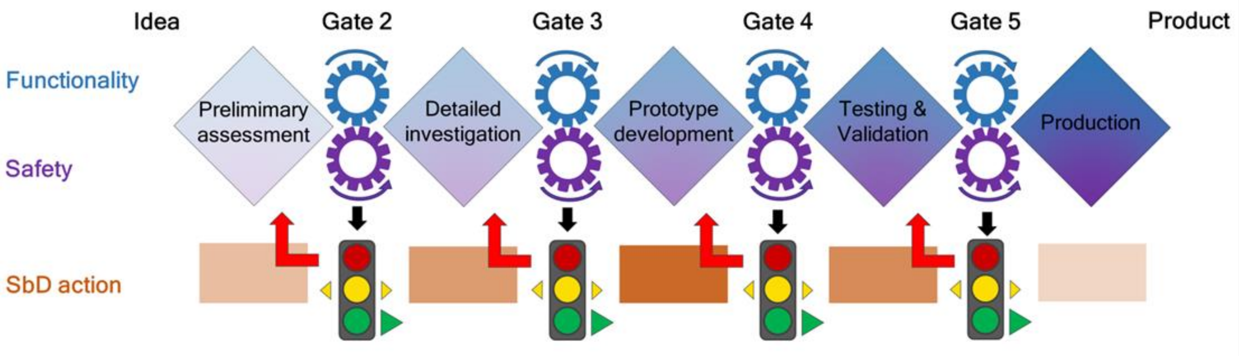

Figure 4: The "Safe-by-Design" principle

NanoReg2

The priciples of "Safe-by-Design" (SbD) ensure that nanomaterials are designed with safety and environmental considerations from the outset. This approach paves the way for safer and more sustainable applications in all sectors.

Project: https://doi.org/10.3030/646221

Duration: 2015 – 2019

Funding: EU Horizon 2020

Publication: Tavernaro I, Dekkers S… Kraegeloh A et al., Safe-by-Design Part II: A Strategy for Balancing Safety and Functionality in the Different Stages of the Innovation Process. NanoImpact 24 (2021) 100354; https://doi.org/10.1016/j.impact.2021.100354

C Development of a digital infrastructure for nanosafety data (Research data infrastructure)

Research data should be considered cultural posessions, as their collection is laborious and often paid for through public funding. While data storage for open-access is already common in some research fields that produce large amounts of data, such as climate science, other research fields still lag behind. We are working on establishing a database that allows public access and subsequent use of our nanosafety data.

Traceability and reliability: Quality standards for data in nano safety (NanoS-QM)

The safety assessment of deliberately produced nanomaterials is a highly complex process to which researchers from different disciplines contribute. Large amounts of data and descriptive metadata are generated which – provided they meet qualitative requirements and are described in detail – can be reused for the research and development of nanomaterials and nanoproducts as well as for predictions and risk assessment in a regulatory context. Possible health effects of newly developed nanomaterials can be identified more quickly, unnecessary repetition of experiments are avoided and the development of new, animal-free methods advances. Researchers have determined which criteria interdisciplinary data and the associated metadata must fulfill in order to be used for the investigation of nanosafety.

Project: Entwicklung und Erprobung von Kurationskriterien und Qualitätsstandards von Forschungsdaten

Funding: Bundesministerium für Bildung und Forschung (BMBF)

Duration: 2019 - 2021

Project: Linda Elberskirch, Kunigunde Binder, Norbert Riefler, Adriana Sofranko, Julia Liebing, Christian Bonatto Minella, Lutz Mädler, Matthias Razum, Christoph van Thriel, Klaus Unfried, Roel P. F. Schins & Annette Kraegeloh, Digital research data: from analysis of existing standards to a scientific foundation for a modular metadata schema in nanosafety. Part Fibre Toxicol 19, 1 (2022). https://doi.org/10.1186/s12989-021-00442-x

D Promotion of public discourse on nanosafety issues (Explain)

The public discussion about the chances and risks of nanoproducts has started only recently and is subject to change as new ideas add to existing conceptions. The Leibniz Research Alliance Nanosafety deals with the question of how the public can be supported in the formation of an informed opinion on this recent and ambiguous research area. While it promises to innovate science in a way that will facilitate greater control of natural processes that affect our very lives, it causes anxiety and vague concerns about safety issues.

Therefore, it is vital to further public discourse by creating opportunities to communicate and exchange information and opinions about nanosafety. This can be realised using digital and traditional media (e.g. the internet and television), or by mounting topic-specific exhibitions in museums. Both approaches try not only to impart factual knowledge but also to encourage people to deepen their understanding of complex and controversial issues.

Figure 5: Results from eye-tracking measurements on a fictional text on nanoparticles that contains contradictory information. The heat map shows the viewing time of the different parts of the website. It was generated by researchers of IWM in a cooperative research project. [Steffen Gottschling]

Study on the understanding of complex information using the example of nanoparticles

In December 2018 a scientist from the Leibniz Institute of Knowledge Media in Tübingen, which is a partner of the Leibniz Research Alliance Nanosafety, conducted a study with nanomaterial experts at the INM. Aim of the study is to compare the comprehension and evaluation of complex and inconsistent informations. Questionnaires were combined with results from eye-tracking measurements on a text on nanoparticles. The results, that will probably be ready by summer 2019, will help scientists to communicate their work in a comprehensive manner and to avoid misunderstandings when discussing data with laypersons.

Funding: This study was partly financed by the Leibniz Research Alliance Nanosafety and the Leibniz Association.

Publication: Kammerer Y et al., The Role of Internet-Specific Justification Beliefs in Source Evaluation and Corroboration During Web Search on an Unsettled Socio-Scientific Issue. J Edu Comput Res 59:2 (2021) 342; https://dx.doi.org/10.1177/0735633120952731

Important publications

The publications chosen for this list are direct results from the cooperations of the research work of the Leibniz Research Alliance Nanosafety.

A Clarification of the mechanisms of action of nanomaterials and their effects on human health

Schmitz C, Welck J, Tavernaro I et al., Mechanical strain mimicking breathing amplifies alterations in gene expression induced by SiO2 NPs in lung epithelial cells. Nanotoxicology 13:9 (2019) 1227; https://doi.org/10.1080/17435390.2019.1650971 **(INM, IfADo, UdS)**

Stöckmann D, Spannbrucker T, Ale-Agha N et al., Non-Canonical Activation of the Epidermal Growth Factor Receptor by Carbon Nanoparticles. Nanomaterials 8:4 (2018) 267; https://doi.org/10.3390/nano8040267

Kraegeloh A, Unfried K, The Safety of Nanomaterials on Molecular and Cellular Scale. in: The Nanomaterials Handbook, Second Edition, edited by Yury Gogotsi, 2017, CRC Press; https://doi.org/10.1201/9781315371795-22

Gomes SIL… Pokhrel S, Mädler L et al., Advanced machine learning techniques on in vivo biological responses to a TiO2 NP library (UV and non-UV exposure) – 11 Fe-doped TiO2 NPs, 122 NP descriptors (atomistic and mesoscopic modelling), 44 biological measures. Nanoscale 13 (2021) 14666; https://doi.org/10.1039/D1NR03231C

Peng G… Mädler L, Pokhrel S et al., Redox Activity and Nano-Bio Interactions Determine the Injury Potential of Metal Oxide Nanoparticles towards Zebrafish, ACS Nano 14 (2020) 4166; https://dx.doi.org/10.1021/acsnano.9b08938

Bredeck G, Kämpfer AAM, Sofranko A et al., Effects of Dietary Exposure to the Engineered Nanomaterials CeO_2, SiO_2, Ag, and TiO_2 on the Murine Gut Microbiome. Nanotoxicology 15:7 (2021) 934; https://doi.org/10.1080/17435390.2021.1940339

Busch M, Kämpfer AAM, Schins RPF, An Inverted in Vitro Triple Culture Model of the Healthy and Inflamed Intestine: Adverse Effects of Polyethylene Particles. Chemosphere 284 (2021) 131345; https://doi.org/10.1016/j.chemosphere.2021.131345

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Kämpfer AAM, Busch M… Schins RPM, Model Complexity as Determining Factor for In Vitro Nanosafety Studies: Effects of Silver and Titanium Dioxide Nanomaterials in Intestinal Models. Small 17:15 (2021) 2004223; https://doi.org/10.1002/smll.202004223

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WELDOX II Study Group, van Thriel C et al., Are Multitasking Abilities Impaired in Welders Exposed to Manganese? Translating Cognitive Neuroscience to Neurotoxicology. Arch Toxicol 91:8 (2017) 2865; https://doi.org/10.1007/s00204-017-1932-y

Rossner C, Fery A, Planet-satellite nanostructures from inorganic nanoparticles: from synthesis to emerging applications. MRS Commun 10 (2020) 112; https://doi.org/10.1557/MRC.2019.163

Peuschel H, Ruckelshausen T, Cavelius C, Kraegeloh A, Quantification of Internalized Silica Nanoparticles via STED Microscopy. BioMed Res Int (2015) Article ID 961208; https://doi.org/10.1155/2015/961208

Astanina K, Simon Y, Cavelius C, Petry S, Kraegeloh A, Kiemer AK, Superparamagnetic iron oxide nanoparticles impair endothelial integrity and inhibit nitric oxide production. Acta Biomater 10 (2014) 4896; https://doi.org/10.1016/j.actbio.2014.07.027

Corrigendum to “Superparamagnetic iron oxide nanoparticles impair endothelial integrity and inhibit nitric oxide production” Acta Biomater 12 (2015) 363; https://doi.org/10.1016/j.actbio.2014.11.009

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van Berlo D, Wilhelmi V, Boots AW, Hullmann M, Kuhlbusch TAJ, Bast A, Schins RPF, Albrecht C, Apoptotic, inflammatory, and fibrogenic effects of two different types of multi-walled carbon nanotubes in mouse lung. Arch Toxicol 88 (2014) 1725; https://doi.org/10.1007/s00204-014-1220-z

Kucki M, Cavelius C, Kraegeloh A, Interference of silica nanoparticles with the traditional Limulus amebocyte lysate gel clot assay. Innate Immunity 20:3 (2014) 327; https://doi.org/10.1177/1753425913492833

Büchner N, Ale-Agha N, Jakob S, Sydlik U, Kunze K, Unfried K, Altschmied J, Haendeler J, Unhealthy diet and ultrafine carbon black particles induce senescence and disease associated phenotypic changes. Experimental Gerontology 48:1 (2013) 8; https://doi.org/10.1016/j.exger.2012.03.017

B Design of safe nanomaterials

Kraegeloh A, Suarez-Merino B, Sluijters T, Christian Micheletti, Implementation of Safe-by-Design for Nanomaterial Development and Safe Innovation: Why We Need a Comprehensive Approach. Nanomaterials 8:4 (2018) 239; https://doi.org/10.3390/nano8040239

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Tavernaro I, Dekkers S… Kraegeloh A et al., Safe-by-Design Part II: A Strategy for Balancing Safety and Functionality in the Different Stages of the Innovation Process. NanoImpact 24 (2021) 100354; https://doi.org/10.1016/j.impact.2021.100354

C Development of a digital infrastructure for nanosafety data

Binder K et al., Discussion on Existing Standards and Quality Criteria in Nanosafety Research – Summary of the NanoS-QM Expert Workshop. (2020); https://doi.org/10.5281/zenodo.4584789

Elberskirch Linda, Binder K Riefler N, et al., Digital Research Data: From analysis of existing standards to a scientific foundation for a modular metadata schema in Nanosafety. Particle Fiber Toxicology 19:1 (2022); https://doi.org/10.1186/s12989-021-00442-x

D Promotion of public discourse on nanosafety issues

Kammerer Y et al., The Role of Internet-Specific Justification Beliefs in Source Evaluation and Corroboration During Web Search on an Unsettled Socio-Scientific Issue. J Edu Comput Res 59:2 (2021) 342; https://dx.doi.org/10.1177/0735633120952731

Gottschling S, Kammerer Y, Thomm E, Gerjets P, How Laypersons Consider Differences in Sources' Trustworthiness and Expertise in their Regulation and Resolution of Scientific Conflicts. Int J Sci Ed B 10:4 (2020) 335; https://doi.org/10.1080/21548455.2020.1849856

Gottschling S, Kammerer Y, Gerjets P, Readers' Processing and Use of Source Information as a Function of Its Usefulness to Explain Conflicting Scientific Claims. Discourse Process 56:5-6 (2019) 429; https://doi.org/10.1080/0163853X.2019.1610305

Selected events

Nanosafety 2013: International Konference, 20.-22.11.2013 in Saarbrücken, Germany

Nanosafety 2017: International Konference, 11.-13.10.2017 in Saarbrücken, Germany
Special Issue: Nanosafety 2017, in Nanomaterials; https://www.mdpi.com/si/11303

Standards und quality criteria in nanosafety research: Workshop as part of the NanoS-QM-Project, June 2020, https://doi.org/10.5281/zenodo.4584789

Nanosafety 2020: International Konference, 5.-7.10.2020, virtuell

Leibniz im Bundestag: 2017 (INM) & 2019 (IfADo)