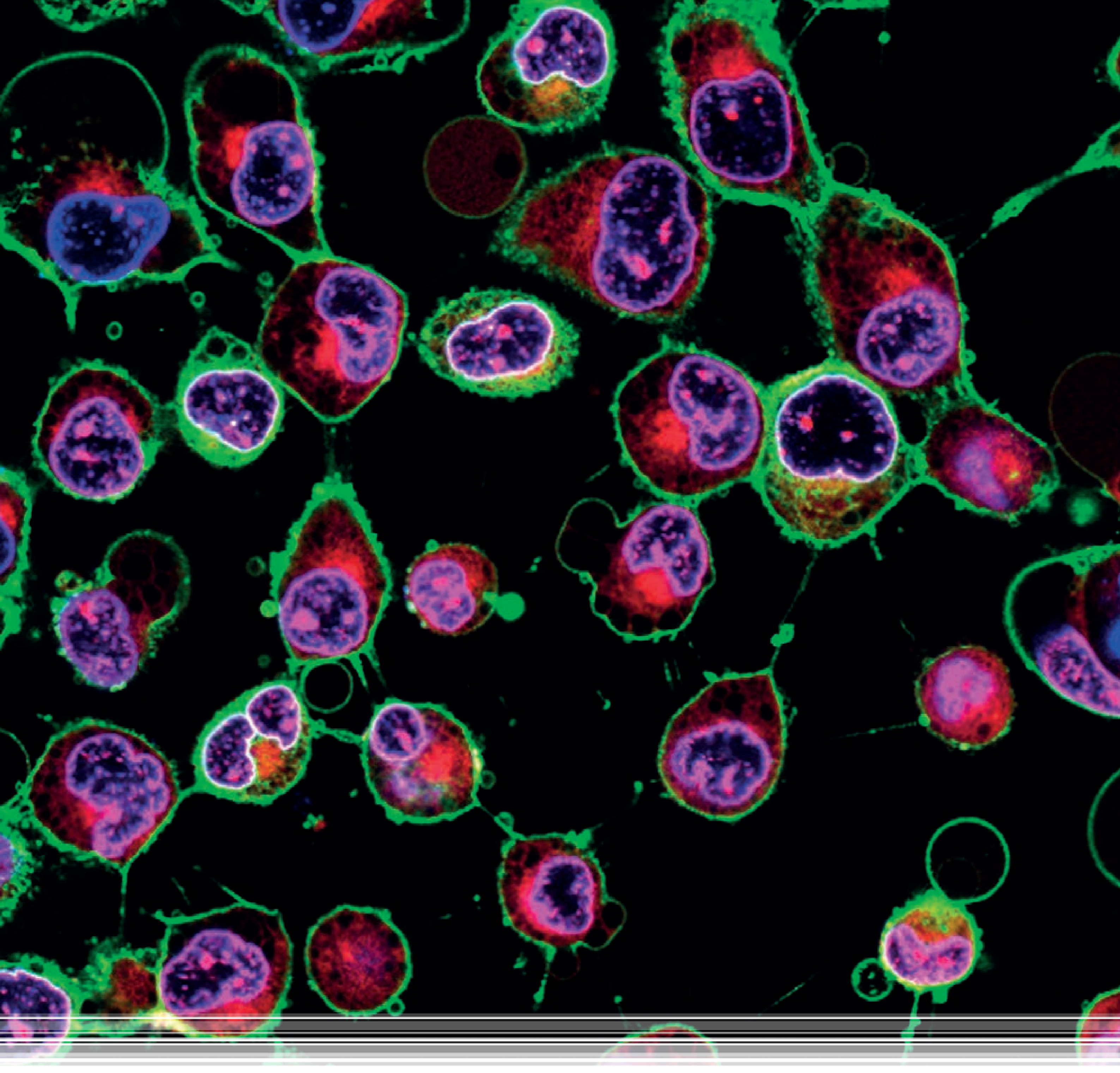

National Research Programme NRP 64

Opportunities and Risks of Nanomaterials

Results, Outcome and Perspectives – Final Brochure

Opportunities and Risks of Nanomaterials
National Research Programme NRP 64

Swiss National Science Foundation

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Cover: High concentration of liposomes in cancer cells.
Photograph page 4: Light-activated nanohpharmaceuticals (in red) accumulated in cancer cells.

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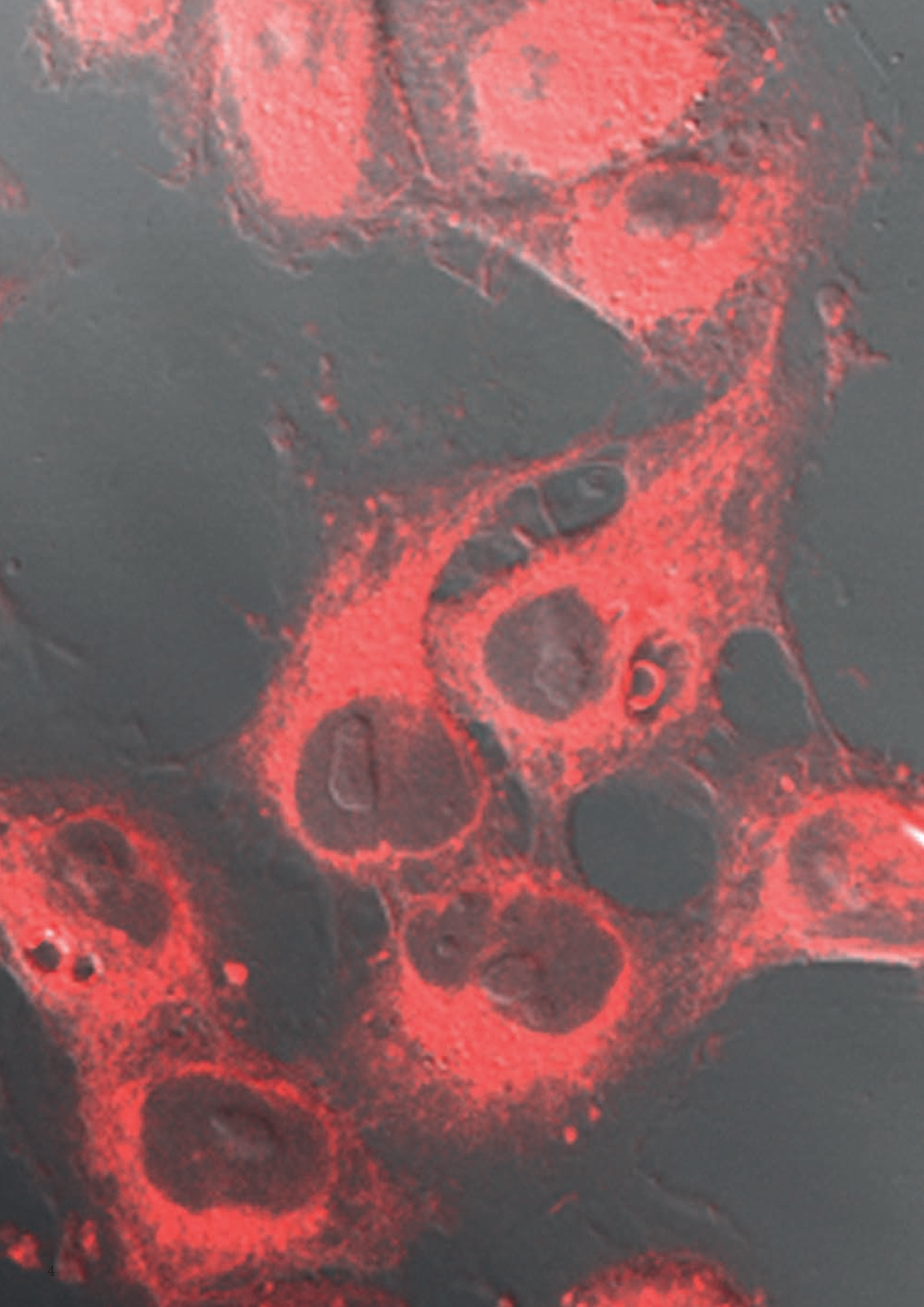


INTRODUCTION

Five years of research, 23 research groups with a total of 111 researchers, 150 publications to date, numerous prizes and awards. The National Research Programme «Opportunities and Risks of Nanomaterials» (NRP 64), got off the ground at the start of 2010 with a blanket loan of 12 million Swiss francs and represented a venture of considerable significance. And it pursued an ambitious goal: understanding how the special characteristics of synthetic nanomaterials could be tapped into, yielding maximum profit, while at the same time remaining as risk-free as possible.

Synthetic nanoparticles have long since become a part of everyday life, even if we are not always aware of it. They are hidden in the most diverse range of consumer goods, such as electronics, textiles and cosmetics, in food, sports equipment and building materials. They ensure that our spices do not clump up, that our chocolate icing has that mouth-watering shine and our French dressing is as white as snow. They make sweaty socks odour-free and make bicycle frames ultra-light but ultra-strong, too. And last but not least, in the medical field, their targeted use aims at ensuring that a treatment is more accurate while having fewer side effects.

Nanoparticles hold great promises. The fact that many substances show a completely different behaviour when they are present as minute particles, was already known before NRP 64. Gold nanoparticles, for instance, change colour due to a physical change: the master glaziers in the middle ages already knew that by adding tiny gold particles to the melting pot, their church windows would radiate a glorious ruby red. It is these special material properties that make synthetic nanomaterials so extremely interesting for research and for the development of new materials and applications. However, reliable knowledge as to what extent the unique nature of these nanoparticles may also pose a potential risk to humankind and environment, has been hard to come by up to now.

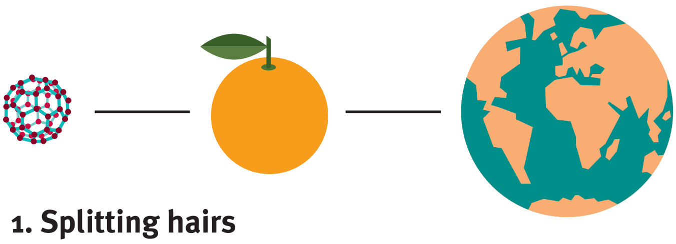
Research groups involved in NRP 64 have taken a closer look. They examined which opportunities and which risks were connected with synthetic nanomaterials: in foods, in nano-based construction and insulation materials, in energy technology and in particular, in the medical field. They analysed in which phase of their life cycle – in the fabrication, during the use, or, at the point of disposal – nanoparticles could pose a risk to the environment or to human health. To do so the researchers developed and tested various measuring methods and measuring devices, experimented with new applications and made astonishing discoveries. For example, that it is frequently enough to just make a minute change to the particle's surface to end up with fundamental changes in their characteristics.

After five years of intensive interdisciplinary research, the increasingly interconnected Swiss nano research community has reached the conclusion that the opportunities that synthetic nanomaterials present, outweigh the risks. Or more precisely: that accurate knowledge about synthetic nanomaterials can aid in making use of these materials' unique properties so as to transform any existing hazard potential into yet further opportunities. At the same token, NRP 64 – and this is of equal importance – also clearly shows where knowledge gaps still do exist and where additional research efforts must be undertaken. And, that sustainable innovation and safety research have to go hand in hand.

Because nanotechnology, as a versatile interdisciplinary technology, will be around in future. The knowledge gathered by NRP 64 will significantly contribute to exploiting its use-potential for the economy, technology, life science and society at large, without this posing any risks to us or the environment. The following pages give you an overview of the most important highlights, insights and recommendations to industry and regulatory entities with regard to a suitable handling of nanomaterials from the point of fabrication, to use in practice, right down to their disposal.

WHAT IS NANO?

Nanomaterials: An overview of the basics



1. Splitting hairs

Nano originates from the Greek word for gnome and the clue is in the word: nanoparticles are extremely small. How small these nanoparticles actually are in reality, goes beyond our comprehension. Or, are you truly able to visualise the statement «A thousand times smaller than the breadth of a hair»? The following comparison may be easier to imagine: using an orange for the purpose of demonstration, a nanoparticle is the same size as an orange is in relation to Earth.

Metre (m) = 1 m

Millimetre (mm) = 0.01 m (10^{-3})

Micrometre (µm) = 0.000001 m (10^{-6})

Nanometre (nm) = 0.000000001 m (10^{-9})

Picometre (pm) = 10^{-12} m
The scale of atomic structures: electrons

Femtometre (fm) = 10^{-15} m
Dimensions of nuclear material: protons

Attometre (am) = 10^{-18} m
The scale of quarks

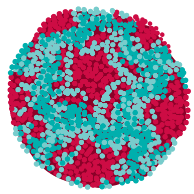
2. Counting peas

One pea may look much like another. The term nanoparticles, by contrast, summarizes the smallest particles of the most diverse shapes and sizes, which in addition also may have vastly differing chemical, physical and topological properties. Nanoparticles come in different shapes – cube, sphere, cylindrical, platelet, or fibre; water-soluble or not.

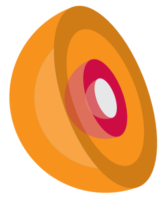
Chemical differentiation:

Organic nanoparticle: e.g. liposomes, polymer vesicles

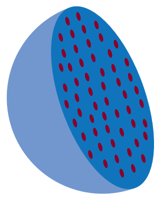
Inorganic nanoparticles: fullerenes; nanotubes, carbon black (industrial soot) as modification of carbon; metals and metal oxides, semiconductors (e.g. silicone)



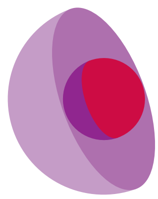
virus-like nanoparticle



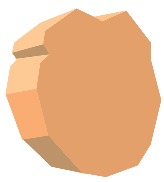
liposome



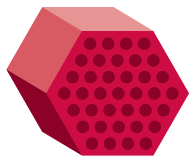
nanosphere



metallic nanoparticle



nanoplate



silica

3. Nanos on the door step

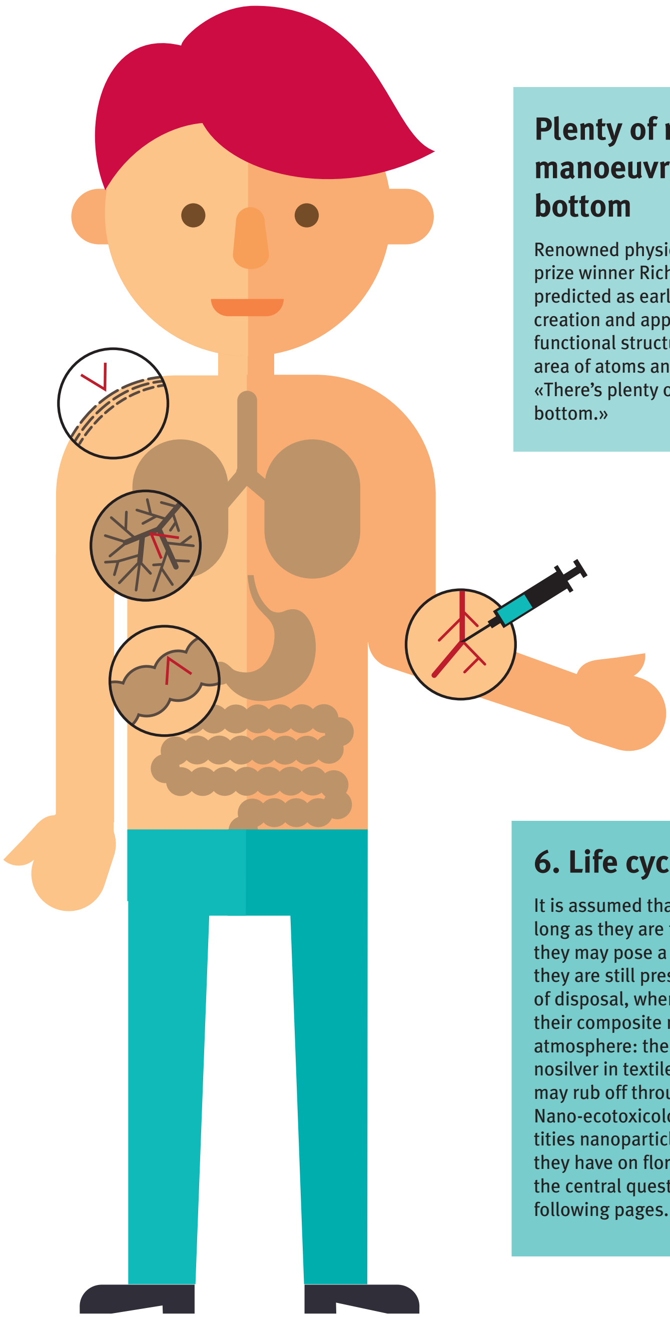
Nanotoxicology examines what consequences result from humans or animals and plants coming into contact with synthetic nanoparticles. Nanoparticles are so small that they can pass through cells and tissue unhindered. Nanoparticles enter the human body via four main entry points:

Via the skin: (undamaged) skin, covered by several layers of dead skin [horn] cells, has a very good barrier function that normally prevents even the smallest particles from passing through to enter living skin cells and ultimately end up in the blood stream.

Via the lungs: The lung with its fine fractal branching out of its airway structure, ending in millions of pulmonary alveoli, is the main point of entry. Once nanoparticles are deposited in the pulmonary alveoli they are able to enter the blood stream, which then distributes them around the entire human organism.

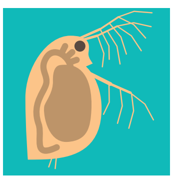
Via the digestive tract: besides the skin, the digestive tract, and in particular the intestinal mucosa, represent another tissue barrier. If nanoparticles overcome this barrier, they will yet again be able to enter the blood stream and will be transported around the whole organism.

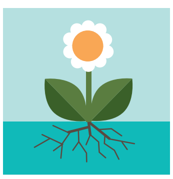
Via the blood circulation: nanoparticles may enter the blood circulation as a result of injections. The blood is therefore an «artificial», but nonetheless important point of entry.



Absorption via environmental organisms

Animals and plants may absorb nanoparticles through the water, the soil or the air.



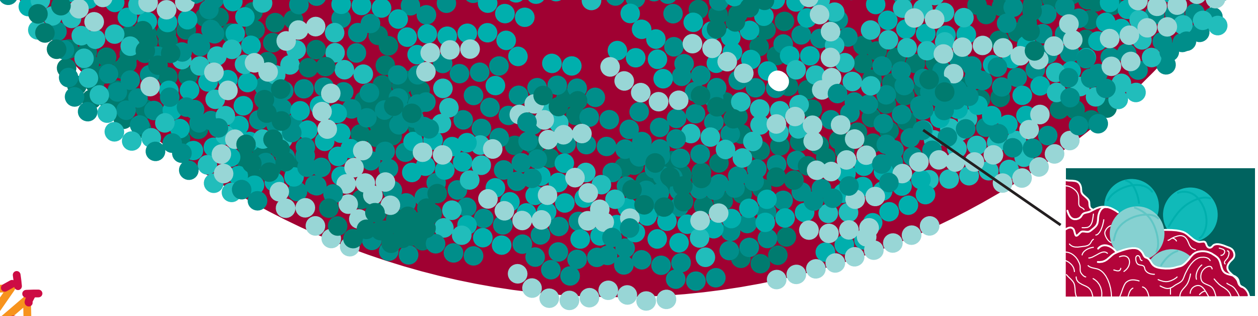


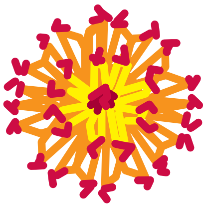
Plenty of room to manoeuvre at the bottom

Renowned physicist and Nobel prize winner Richard Feynman predicted as early as 1959 the creation and application of functional structures in the area of atoms and molecules: «There's plenty of room at the bottom.»

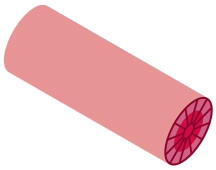
6. Life cycle

It is assumed that nanoparticles do not represent a threat as long as they are firmly integrated within a material. However, they may pose a risk during the production process, while they are still present in loose form, during use or at the point of disposal, when they may potentially be set free again from their composite material condition and released into the atmosphere: the nano-titanium dioxide in façade paints or nanosilver in textiles may wash out, nanocarbon tubes in plastics may rub off through wear-and-tear and may become air-borne. Nano-ecotoxicology is concerned with how and in which quantities nanoparticles enter the environment and what effect they have on flora and fauna, on rivers and soil. This was also the central question in the NRP 64 projects described on the following pages.

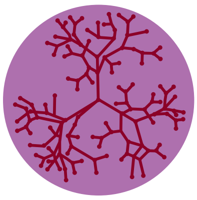




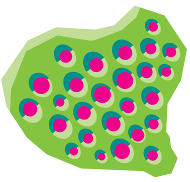
micellar nanoparticle



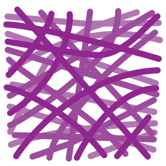
nanotube



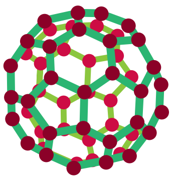
dendrimeric nanoparticle



porous nanoparticle



nanofibres



carbon-based nanoparticle

4. On the surface of it...

Viewed from space, our planet earth appears like a smooth ball. But as we know: its surface has mountains, level planes, deserts with dunes and fissured valleys. And the surface of nanoparticles may be just as multi-facetted. In ultra-small nanoparticles for instance, up to 50 % of its atoms reside on the surface – this allows proteins to attach themselves. The effect of such surface phenomena is often more important than the physical processes that take place inside the nanoparticles. It is an established fact that nanoparticles, as soon as they get into contact with biological systems, are immediately covered by a whole garland of proteins. This protein corona influences the interplay between nanoparticles and their surroundings, for example the interplay with living cells.

The surface make-up and the large surface area of nanoparticles in relation to their mass are, besides their size, important reasons for their particular behaviour within biological systems. Nanoparticles are for instance very adept at entering living cells and prompt a reaction there.

It is hoped that these new nano-specific characteristics can be seized upon by R&D to be utilised for innovative applications: by altering the surface of synthetic nanoparticles in a targeted way, it is for example possible to improve their stability, their aqueous solubility, or control their effect.

However, it is exactly because of this altered interplay with their surroundings, that nanoparticles can also become a risk to health and the environment.

5. On a mission

Synthetic nanoparticles are artificially created particles on a nano-scale, which have been specifically equipped with new characteristics and functionalities. Frequently, they are integrated into solid, liquid or powder-based materials to serve a specific application purpose.

Such engineered nano-troops, when deployed on a mission, have multiple fields of application. They are used, for example, in the area of consumer goods (foods, textiles, cosmetics, sports and leisure articles), in material production (building materials, automotive industry), in the environment (agriculture, energy generation and storage, waste-water treatment and sewage systems) and in medicine.

EU definition: In 2011 the EU commission submitted its first recommendation for a framework definition of nanomaterials: Any material which contains particles in unbound condition, as aggregates or agglomerates and in which at least 50 % of the particles have at least one dimension of a size that ranges between 1 and 100 nanometres, are classed as nanomaterials.

CHEMISTRY
- substance research
- synthesis/catalysis
- sensors
- process monitoring

MEDICINE/ HEALTH
- diagnostics
- therapy
- targeted drug release

CONSUMER PRODUCTS
- cosmetics
- sun screen
- bactericidal textiles
- packaging

ELEKTRONICS
- electronic paper
- displays
- accumulators
- sensors
- biochips

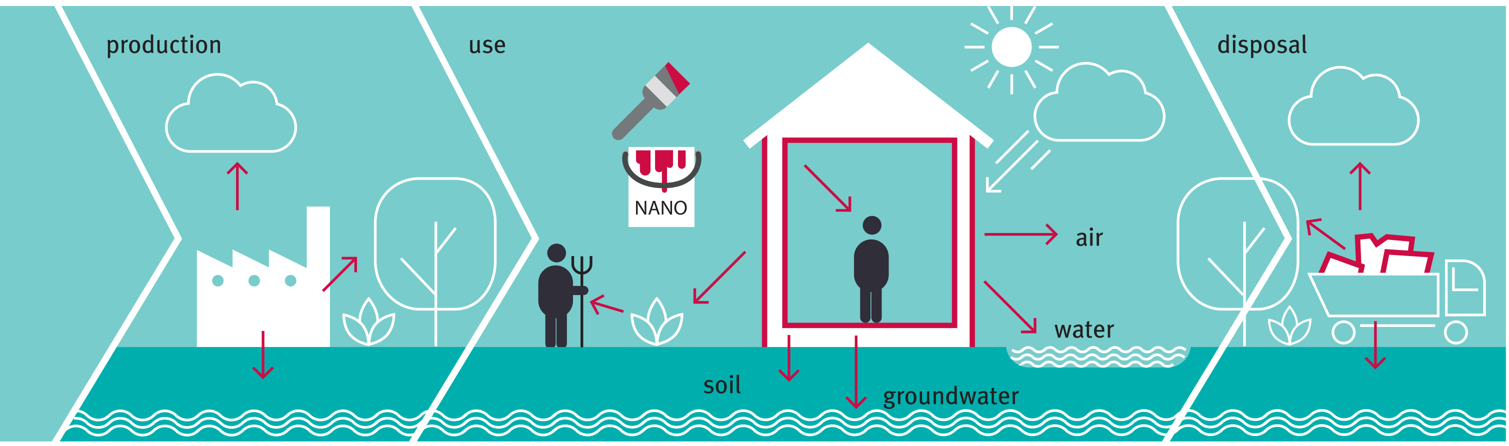
ENVIRONMENT
- wastewater treatment
- photocatalysis
- environmental monitoring

ENERGY
- batteries
- fuel cells and solar cells

OPTICS
- photonics
- optical systems
- light technology

CONSTRUCTION
- improvement of building materials (mechanical properties)
- clean surfaces
- isolation
- corrosion resistance

AUTOMOBILE
- scratch-resistant paints
- foams and polymers
- corrosion resistance
- sensors
- catalysis (combustion, exhaust gases)



HOW HARMLESS ARE THESE NANOS?

Even if the opportunities outweigh the risks: any indications of potential risks must be thoroughly investigated – an overzealous regulation, however, would be counterproductive.

Because they are so miniscule, but more importantly, because of their chemical and physical characteristics, nanoparticles interact in a rather versatile and complex way with their surroundings. A garland of proteins adheres to the tiny particles as soon as they enter a biological system, for example the human body. Like a camouflage suit, this protein corona alters the identity and mechanism of the particles. Exactly how these nanoparticles pass through biological barriers, which routes they take, whether they gather within tissues or whether they are excreted again at the end, was examined by various NRP 64 projects. Central to all of these was one key question: Do synthetic nanoparticles pose a risk to health?

When nanoparticles are inhaled, they are very efficient deposited on the surface of the lungs. What happens next is what interests *Marianne Geiser Kamber* from the Institute for Anatomy at the University of Berne, and in particular, after unintentional inhalation when using consumer goods that are already available on the market: the impregnation spray for shoes, which contains nanoparticles, for instance. Because especially in the case of this product, particularly susceptible sections of the population may be affected: children, pregnant women, the elderly or people that already suffer from a respiratory illness, such as asthma sufferers: «These are the people we need to protect and any laws and regulations must be aimed at them», says Geiser.

Deep inside the lungs

Led by Marianne Geiser, an interdisciplinary group developed an *in vitro* measuring chamber, which allows a lifelike examination of the effect that different nanoparticles deposited on the surface of the airways have on both healthy and diseased cells. With the aid of this portable test system that can be connected to any particle source, the team around Marianne Geiser was able to show that, in healthy people, the surface of the airways –a highly differentiated tissue with its cilia and complex cell layers – reacts effortlessly towards these tiny invaders . The question remains as to the potential effect of a continued exposure. «We have an enormously robust cleaning system in our lungs. But we may also overburden it», says Geiser.

That is particularly true, when the air in the workplace is prone to heavy nanoparticle loads.

Michael Riediker from the Institute for Work and Health at the University of Lausanne simulated inside an inhalation chamber, what happens when workers inhale nanoparticle-laden metal vapour, which is a by-product of the welding process. He found signs of oxidative stress inside the blood, the urine and in the expired breath – proof that particles present in the welding vapour cause a stir inside the lungs' cellular defence mechanism: «No healthy individual will fall over and die, but these welding vapours are certainly just as damaging to a person's health as smoking is to a smoker or the health risks of someone living in a polluted city», explains Riediker. Taking concrete protective measures at the workplace is certainly called for.

For a better silica flow

Nanoparticles also enter the human body via stomach and intestines. Moreover, they do not always do what they are meant to do there. *Hanspeter Nägeli* from the Institute of veterinary pharmacology and toxicology at the University of Zurich wanted to investigate with his project, how certain food additives containing nanoparticles would affect the immune system of the intestines. He used silica particles as a neutral reference substance. They

Michael Zimmermann
ETH Zurich

are regarded as safe and are routinely added to foods in powder form (E551) to ensure that the ready-made soup and the seasoning do not clump up. Contrary to expectation, however, it was not the metal oxide particles – such as titanium dioxide that gives the French salad dressing or toothpaste its beautiful white shine – that put the dendritic cells of the intestinal mucosa into high alert, but the anti-clump substance. It is these cells, imbedded inside the intestinal mucosa, which are the first to detect any foreign materials and which, if need be, trigger an inflammatory or immune reaction against any disease-causing germs. The dendritic cells for the *in vitro* trials were taken from bone marrow stem cells of mice – it is therefore not yet possible to draw reliable conclusions for human exposure. Despite of this, Nägeli recommends a new assessment for the use of silica particles as a systematic food additive.

A partial removal of this warning was issued by *Michael Zimmermann* from the Institute for Food, Nutrition and Health at the ETH Zurich. Using intestinal cell lines and in animal studies, he examined whether the consumption of food that has been enriched with nano-structured iron compounds, could be damaging to health. Iron deficiency is the most common diet-related ill-health in the world – almost a third of the world's population suffers from iron deficiency. Enriching food with iron could possibly represent an effective strategy, but is relatively difficult to achieve with the iron substances available today. Because of this, the prospect of reducing iron compounds to nanometre dimensions heralds a new generation in ferrous iron-additives that can be absorbed quickly and are neutral in taste, and has met with huge interest by the food producing industry: «Everybody is now waiting to hear if it is safe beyond doubt», says Zimmermann. His studies indicate that it is – at least in animals: no signs of oxidative stress in the cell studies, no iron accumulation or tissue damage in the test animals. Instead, first findings indicate that nano-iron compounds do not slip through any secondary gates, but follow the same absorption path as iron medication commonly administered with food.

Wide-open doors

But what if nanoparticles do not even have to overcome the body's own defence mechanisms and barriers, because people themselves are implanting them deep inside their bodies due to their highly promising features? *Martin Frenz* from the Institute of Applied Physics at the University of Berne investigated a particularly critical case. For seamless vascular connections in the brain, for example when treating aneurisms, «plasters» enriched with nanoparticles and proteins which are then treated with laser beams, were tested in animal trials: «To visualise the whole process, it is similar to frying an egg», explains Frenz, «the dye in the nanoparticles absorbs the light, which prompts a thermal effect that binds the proteins inside the «plaster» to the vascular wall.» Without the nanoparticles, this glue would not hold. However, what happens to the particles, when the bio-degradable «plaster» dissolves? With the help of an interdisciplinary team made up of biologists, chemists, medical doctors and physicists and with the aid of state-of-the-art optical and electro microscopic methods, Frenz examined how two specific types of nanoparticles spread themselves around the brain tissue and which biological reactions they triggered by doing so. Both types were absorbed by the brain's defence cells and these cells reacted to both types with temporary oxidative stress: «According to what we know at present, we are nevertheless confident in stating that the probability that this results in cell damage is relatively small», states Frenz. For him it is obvious: «The possibility that this seamless vascular connection will one day be possible in human medicine as well is greater than any risks.»

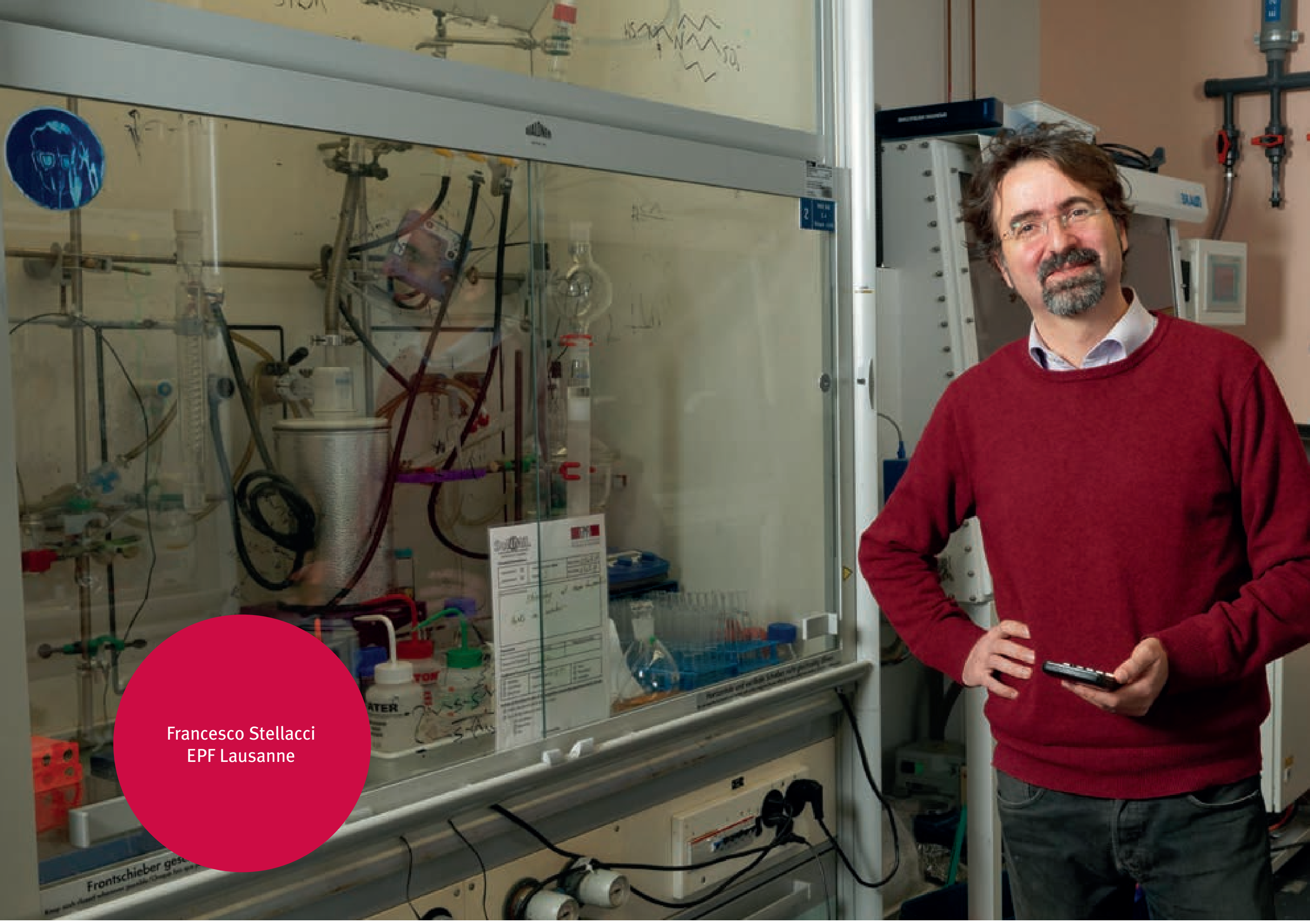
WHEN RISK TURNS INTO AN OPPORTUNITY

NRP 64 shows that investigating risks results again and again in new application opportunities.

That nanoparticles can get anywhere and can even overcome cell barriers, makes them a potential health hazard. However, this can also be harnessed in positive ways. Empa [Swiss Federal Laboratories for Materials Testing and Research] researcher *Peter Wick* investigated in his NRP 64 project, how nanoparticles get from mother to unborn child via the placenta. In cooperation with the University Hospital Zurich and thanks to human placentas kindly donated, his team simulated the mother-foetus circulation in the laboratory. They injected polystyrene particles of various sizes and with varying surface loading on the mother's side of the placenta and then observed which ones of these would overcome the placenta barrier, how and how fast they would manage this, how they would enter the placental tissue, and how they would spread around the placenta and influence its cell functionality. Unsurprisingly smaller particles are better at penetrating the placenta barrier than larger ones. However, the values are not identical for all nanoparticles, since they vary according to size, chemical make-up and surface loading: «How these three factors are linked and which transport mechanisms are at play exactly, is presently not possible to tell», explains Wick. But besides many yet unanswered questions, many promising possibilities for nanomedical applications are looming on the horizon. For example, in medication whose active ingredients are intended for the mother alone and which could be harmful to the unborn child, one could bind the active ingredient to nanoparticles of which one is certain that they cannot penetrate the placenta. On the other hand, health problems could already be treated inside the placenta prior to birth, thereby reducing the risk of premature delivery. These are, of course, dreams of the future, as it requires many more years of intensive research.

Catching the burglar at the door

The conclusion that Peter Wick draws from the NRP 64 project is the realisation that merely focussing on the potential harmfulness of synthetic nanoparticles, is the wrong approach: «Instead the question ought to be: „Can we produce them in such a way that their use value outweighs the risks?» Moreover, this is exactly what *Francesco Stellacci* from the Institute of Material Sciences at the EPFL in Lausanne has done. The goal of his project was to copy nature and to alter nanoparticles in such a way that they would transport medication right to the target and inside of certain cells without causing any damage to the cell's membrane. The same way that a virus channels its genetic material to a cell where it then takes over the command. For this research project, the research team around Stellacci encased gold nanoparticles in a water-repellent and water-binding coating consisting of organic molecules. The team was able to show that it takes only miniscule alteration in the molecule surface arrangement to neutralise the nanoparticles' toxicity. However, the reciprocal effect between nanoparticles and viruses held an even bigger surprise for Stellacci's team: here it became apparent that certain particles can be used to suppress viral infections. Stellacci explains how this is done: «The virus is like a burglar who wants to get inside the house. The viral drugs currently available catch the thief when he is already in the house and after he has had time to make a mess. The nanoparticles by contrast, apprehend him right by the front door and before he gets inside.» The prospect of one day being able to effectively combat viral diseases in much the same way as bacterial infections are today successfully treated with antibiotics – and potentially treating such deadly epidemics as the Zika virus, Ebola or



Francesco Stellacci
EPF Lausanne

Dengue fever with the help of nanoparticles – excites Stellacci: «Mind you, the road to a drug being approved is long and arduous.»

Barbara Rothen-Rutishauser, researcher from the Adolphe Merkle Institute at the University of Freiburg, is also making use of the potentially hazardous properties of nanoparticles. Allergic asthma is the result of an overreacting immune system; this overreaction takes place in the exact spot where these nanoparticles end up when they are inhaled: in the small channels of the airways and the lung's alveoli. If one was to load nanoparticles with a dose of medication before they were being set off on their journey to the lungs, one would be able to attack the asthma right at the spot where it causes havoc: efficiently and without side-effects.

That is the final goal. There is plenty to do en route. Barbara Rothen-Rutishauser and her team have conducted whole series of material optimisations, cell experimentations, 3D tissue modelling and animal testing with a material suitable as nanocarrier. They opted for non-toxic gold particles with differing surface loadings. How do lung immune cells behave when they come into contact with this alien body? Are they able to absorb and process these particles and how important is size and surface structure in this scenario? These multi-award winning studies have shown that certain particles are indeed able to trigger an immune reaction in the lymph nodes of mice. What happens to the particles once they have done their job – whether they remain inside the cell or whether they are excreted – remains open to question. In addition, the route from mouse to human is a long one. Nevertheless, Rothen-Rutishauser is for the moment happy to say this much: «Nanomaterials need not induce fear, but one has to use them in a responsible manner. If not meant for medical treatment, I'd rather avoid inhalation.»

Nano therapists

Caroline Maake from the Anatomical Institute at the University of Zurich also wants to deploy these nanoparticles as therapists. Patients who suffer from chronic inflammatory intestinal diseases such as Morbus Crohn or Colitis Ulcerosa, presently depend on medication that causes severe side-effects. If it was possible to package such medicine in biodegradable

nano-capsules and to steer them to the exact place where they are meant to take effect, this would mean a huge gain for gastro-intestinal sufferers. Maake's research is part of the large and still ongoing European ERA NET EuroNanoMed research project. She and her team contributed with microscopic analyses of tissue samples of mice; they investigated which nano-carriers in which size and concentration would be best suited as couriers without causing damage on route, and also explored via which route most of them would reach their target destination. In this, Caroline Maake reached the convincing understanding that the smallest differences in the size of the particles could have huge biological effects. At present, many more hurdles must be overcome, not least due to the financing of the extremely complex admission procedures for drugs, before a nanomedicine, free of any side effects, is available to treat the incurable intestinal diseases that are plaguing ever more people in western countries. Maake is convinced: «In this area, nanoparticles can really achieve something.»

Beatrice Beck Schimmer from the Institute for Anaesthesiology at the University Hospital of Zurich is not likely to contradict her. She uses nano-magnets in her project in order to filter any potentially harmful substances out from the blood, such as metal or proteins produced by cells or pathogens. To do so she packs a whole cleaning squad of antibodies onto highly magnetic carbon-coated iron nanoparticles, whose purpose it is to catch the offending substances. At the end, a magnet filters the particles out of the blood again. The whole cleaning process takes place outside of the body.

Here too, the long-term goal is clinical use in humans. For Beck Schimmer and her team the initial objective was, based on cell models and *in vitro* studies, to find out which particles could be used inside the blood without having negative effects, i.e. without causing for instance blood clots or inflammation. The researchers also took a close look at what happens, when nano-magnets escape and get back into the body with the cleaned up blood, where they then lodge, in the lungs or in the liver. In this study, after a one-year observation period of mice, no inflammatory reactions nor tumour formations were found. The researchers concluded from this that the new blood cleansing process is not only extremely efficient, but also allows estimating the risks: «With this project we successfully managed to bring the foundations for developing a highly promising new technology out of the lab and into the immediate vicinity of the patient», Beck Schimmer is pleased to announce and already envisages further possible uses for nano-magnets: they might be able to filter cells out of the blood or could be loaded with medicines to be transported to a specific organ or precise tissue section.

BIG PROMISES

Where new materials are concerned, high hopes are placed on nanoparticles. Their utilisation is hoped to improve the characteristics and the potential of materials and improve medical application.

Cellulose is the most important building material in the plant world. «Each plant has cellulose fibres of nano-scale dimensions», explains material scientist *Christoph Weder* from the Adolphe Merkle Institute at the University of Freiburg. It is relatively easy to isolate these fibres in a research lab. They are enormously strong, have great tensile strength, are stiff, and make it possible, added as filling material, to produce stronger and more stable, yet lightweight composite materials. These outstanding mechanical characteristics make them very precious for use in the plastics/synthetics industry – what is more, as they are sourced from plant-based waste, they are correspondingly cheap to manufacture.

As a biomaterial, nanocellulose was hitherto classified as harmless to human health – in contrast to, for example carbon nanotubes, which, depending on composition and length, may behave in the same way as asbestos fibres. Within the remit of his NRP 64 project, Christoph Weder investigated whether there really is no risk to human health when nanocellulose accidentally ends up in the lungs during manufacturing, processing, use or disposal of it. In his investigation, he used the 3D lung cell models from his colleague, Barbara Rothen-Rutishauser. The findings give a cautious all-clear signal. Acute reactions did not occur – good news for the scheduled commercialisation of new nanomaterials made from cellulose.

Nanocartilage for worn joints

In cooperation with several research groups, Christoph Weder developed and manufactured as part of his research project various such nanocomposite materials, for example porous materials as ecological alternatives to conventional insulation foams or particularly strong compounds with extraordinary tensile strengths. Not quite according to plan, one doctoral student in her work explored the possibility of using nanocellulose templates to grow artificial cartilage in the lab. Since cartilage damage, which sooner or later results in arthritis and progressive wear-and-tear to the joint, cannot heal in a natural manner, the possibility of creating such a tissue substitute, is of immense interest. The doctoral thesis in question was awarded a prize by the Swiss Chemical Society and Christoph Weder is glad that the SNSF agreed to this deviation from the original project: «Good research needs to be based on trust, not on 'planned economy'», he enthuses.

Not cartilage, but bone replacement materials was the subject matter of the research project of the research team led by *Reto Luginbühl* from the Robert Mathys Stiftung (RMS) in Bettlach. Their aim was to strengthen the ceramic bone cements available today with nanofibres. If bone substance is lost following an accident, a tumour or an operation, the cavities that occur are currently treated with bone grafts or filled with bone replacement material. However, they tend to be so brittle, that they are not suitable for bearing heavy loads. This in turn necessitates the use of plates and screws –this frequently requires a second operation after the healing process in order to remove the foreign objects again. Biodegradable nanocomposite materials that are as stable and capable of load-bearing as healthy bones are, would open up completely new possibilities in this area as well. They could not only serve as a filler material, but could also be used to create plates and screws that dissolve by themselves inside the body once healing is complete.

To produce the nano-fibre-reinforced cement, the research team had to develop a highly complex and protracted procedure, in which fibres spun from absorbable polylactic acid were mixed with nanoparticles and cement powder. First, animal tests did not identify any negative biological effects and the new bone cement is, thanks to its inner workings made of the most filigree of fibres which are homogenously distributed, four times more break-resistant than the non-reinforced material. For Reto Luginbühl there is much more that can be gotten out of this project: «We are not yet where we would like to be with it, but we are on the right track.»

Doping for lithium-ion batteries

In the field of energy storage, nanomaterials may be able to solve many fundamental problems posed by conventional batteries. For example, the size of the powder particles used in today's lithium-ion batteries prevents the discharge of the entire amount of lithium-ions contained inside during the course of the batteries charge-discharge cycle. «If the grain sizes were not of micrometre dimensions, but were to be much, much smaller, then even a lithium-ion residing right in the centre would be able to migrate to the outside

Katharina Fromm
University of Freiburg

and back. Hence, charging and discharging performance of the battery would be more efficient. Plus, a significantly higher amount of active lithium-ions could be packed inside a battery», explains *Katharina Fromm* from the Department for Chemistry at the University of Freiburg. By using nanoparticles, her research team managed to dramatically improve the characteristics of electrode materials currently available on the market. Moreover, using a novel material, the team from Freiburg also managed to reach the maximum possible charging density in coin cell batteries. From the coin cell to car battery and right down to giant batteries as energy storage systems that replace a domestic fuel tank in a family's home that is powered by solar energy – all this would now be feasible and doable with the support of engineering colleges and industry partners. In addition, Katharina Fromm is convinced that it would also be economical in the long run, both for industry and the environment.

Lithium-ion batteries are the bearer of hope for energy supply, network storage and for electric mobility finally seeing a market breakthrough. However, for this to become reality they must become more powerful and more reliable. The project of *Vanessa Wood* from the Institute for Integrated Systems at the ETH Zurich is making a huge contribution in this field. She has developed a new method using synchrotron X-ray absorption spectroscopy to examine on an atomic level how lithium-ions migrate from negative to positive electrode during charge and discharge. In many of the commercially available batteries, this process is relatively slow. That it can be accelerated if the active material is made of nanomaterial, is no secret. Unfortunately, reducing the particle size also harbours certain safety risks as batteries age faster and have a smaller energy density. By fusing nanoparticles into porous micro spheres with the help of a spray drying process in her experiments and simulations, Wood managed to retain the advantage of a shorter diffusion path while simultaneously eradicating undesirable side effects, thereby improving the characteristics of the battery.

Nano is not always better

In many cases, reduction down to the nano-scale bears a tempting potential for innovative applications. But nanomaterials do not always hold their promise. A new generation in wood protection treatment has been a hit on the US market since 2006, where copper carbonate particles replace the conventional-sized copper particles that were previously used: several thousands of tons of this product are sold every year to protect fences and wooden posts against fungus. Because the copper carbonate nanoparticles penetrate deep into the wood, the new impregnation protection is claimed to protect for longer, and is claimed not to pose any health risk to humans or the environment. One of the projects led by Empa researchers *Peter Wick* and *Francis Schwarze* has now discovered that the miracle product does not fulfil its promises and moreover, that it is totally unsuited for Europe's native timber types, such as red spruce and silver fir. That is because the solution hardly manages to penetrate these hard wood types at all: it stays on the timber surface from where it may enter the atmosphere as nano-copper-laden wooden dust as a result of mechanical abrasion. There is the added possibility of copper-resistant fungi absorbing and transforming the nanoparticles and then passing the copper onto the environment via their spores. It cannot be ruled out that it also enters the lungs via wood dust or spores, which may have a detrimental effect on health.

ON LAND AND IN WATER

So that nanoparticles can be used in an eco-friendly way, knowledge is essential about how nanoparticles that are released into soil and into waterways behave.

Mattress protectors, socks, bandage material: silver nanoparticles are used in many products because of their germicidal effect. Not only do they kill off hospital germs, body odour producing bacteria are also no longer safe. The global consumption of nanosilver is estimated to amount to several hundred tons per year. But what if the metal nanoparticles are washed out of the garment and are flushed out into the wastewater? Are they killing off the microbes there as well and thus disturbing the entire water ecosystem? *Ralf Kaegi* from the Eawag (Swiss Federal Institute for Aquatic Research) in Dubendorf was able to show that the great reactivity of the small particles works in favour of the environment in this scenario. Based on sewage water samples and laboratory experiments it could be established that silver nanoparticles in the sewage water immediately connect with other particles and are transformed into the significantly less toxic substance, silver sulphide. «Another factor is that wastewater treatment plants are very efficient at filtering them out again – as well as all nanoparticles in general – so that less than 5 percent actually end up in the surface waters», explains Kaegi. The sewage slurry laden with particles that is left in the treatment plant is burnt in Switzerland, hence it does not represent a new exposure risk for the environment. It would theoretically be possible for new metallic particles to form during the incineration process and enter the atmosphere as ash. Whether this is the case will be Ralf Kaegi's next research project. In the water cycle, by contrast, he concludes from his findings that a nano-specific silver monitoring is not necessary: «For me this means that we can now focus our work on profitable applications», he says and is here referring for example to the chance of using activated carbon, impregnated with silver nanoparticles, in the water filters of countries that historically find it hard to supply their populations with enough clean drinking water.

Trojan horse

Two more NRP 64 projects at the Eawag, from the Department for Environmental Toxicology, also concerned themselves with silver nanoparticles. *Renata Behra* examined how aquatic micro-organisms – bacteria, algae, fungi and tiny snails – cope with nanosilver. She found indications that the particles have a detrimental effect on the biodiversity of these microorganisms, which are vital for a healthy ecosystem. The nanosilver concentration tested was, however, higher than that predicted for the environment. And nanoparticles transformed into silver sulphide –as shown by Ralf Kaegi as being the fate of most silver nanoparticles that pass through wastewater treatment plants into the water – showed toxic effects that were significantly less pronounced.

Kristin Schirmer was interested in how and via which route nanoparticles would interact with plant- and animal cells in water. What she discovered in her *in vitro* experiments had hitherto not been known: while algae possess a protective layer that does not allow even nanoparticles to reach the inner membrane of a cell, the much more permeable cell membrane of fish cells, i.e. the plasma membrane, actively welcomes them via the same mechanism with which human cells tend to do so, for example. «It's just like the Trojan Horse Effect», says Kristin Schirmer, «because this process contributes to the dissolution of silver nanoparticles, while at the same time, the highly toxic silver ions are released inside the cells.» What is more, absorbed silver nanoparticles are able to disturb certain cell functions as they tie themselves to proteins inside the cells.

Diffused light

Whether synthetic nanoparticles cause damage or what kind of damage they may cause once they have entered the environment has so far only partially been explored. The elegant optical *in vivo* measuring method developed, and already patented, by *Olivier Martin* from the Nanophotonics and Metrology Lab at the EPFL (École polytechnique fédérale de Lausanne) allowing a reliable determination of environmental risks posed by nanoparticles is a great step forwards. Using his stress test makes it possible to determine - in real time - the extent of oxidative stress with which living single-celled aquatic organisms react when coming into contact with toxic substances such as nanoparticles – and also to find out, whether they recover again once the exposure is over. As the stress response is measured outside the cell, the measuring method itself has no bearing on the cell's reactions: it is non-invasive and can identify potential negative effects of synthetic nanoparticles on microorganisms in a variety of natural environments, such as in rivers and lakes.

Ironically, the key feature of Martin's portable and hence extremely versatile biosensor is, that it owes its measuring sensitivity to the optical properties of nanoparticles. Cells under oxidative stress excrete hydrogen peroxide – the more stressed they are, the more peroxide they excrete. However, what takes place here in the nano-dimension is barely measurable. The scientists around Martin have therefore made use of a trick: by adding polystyrene pellets in sub-micrometre dimensions they extended the length that the light has to travel inside the sample examined. Thanks to this diffusion, which acts like an optical amplificator, even the most filigree differences become measurable via light absorption. Experiments with the biosensor have shown that single-celled algae release a measurable amount of hydrogen peroxide even when subjected to only the smallest amounts of toxic substances – including nanoparticles.

For Olivier Martin, these results confirm primarily one thing: «We must continue to apply the precautionary principle.» This is because the cells' stress response turns out to be extremely complex: «We can see, for instance, that

the toxicity of the nanoparticles is dependent on the interplay with their environment. Furthermore, we can see that there is a sort of memory effect, i.e. that cells that have already had contact with nanoparticles in the past, react differently upon their second encounter.» For biologists and toxicologists there remains a lot of work to be done in order to interpret correctly the stress responses measured: «It is important not to bury our heads in the sand, but to keep working at understanding these rather complex processes.»

A farmer's little helpers

So much to water. But what about the soil? Agriculture has high hopes for synthetic nanoparticles. Its addition is meant to make fertilizers more effective, pesticides more stable and more eco-friendly – it promises to make it possible to precision-target active ingredients and to transport them to exactly the point where they are meant to act. This would also mean that the dose applied could be reduced, because less of the agent would evaporate, be bleached by the sun or be diluted down by water. Initial agricultural applications in the USA have already been approved and commercialised.

What the deployment of such little helpers would mean for the performance and quality of crop plants and for soil health and soil microorganisms, where they could get to, whether they would and where they would accumulate, are all questions that are still unanswered. The reason for this is not a lack of interest, but because soils are highly complex environments, as *Thomas Bucheli* from the Agroscope (Swiss centre of excellence for agricultural nutrition and environmental research) in Reckenholz, explains: «Nobody in the world today can quantify nanoparticles in the soil – that's simply not possible with the analytical technology available today», says Bucheli. So, should nanoparticle-containing production agents reach the market in the near future, this would cause a major headache for the relevant approval authorities.

In bacteria liquid cultures, hydro-cultures and pot trials with natural soil, Thomas Bucheli carried out exposure, distribution and effect studies on wheat and clover and on various microorganisms essential for plant health. The aim of his project was to make a contribution towards the development of a reliable, standardised test method for clarifying the risk of using nanoparticle in agriculture: «The research community has been working towards this for decades», he says.

Was he successful? According to Bucheli, his project team did certainly manage to provide new technologies and methods for an improved quantification of exposure to synthetic nanomaterials. However, he is cautiously positive when it comes to stating their effectiveness: «So far we did not find any drastic effects on essential soil and fertility functions in our tests», he declares. What is clear for him is that researching the effects of synthetic nanomaterials on a complex natural environment should continue: «What we're doing here is being pro-active. Sooner or later, nanomaterial-containing pesticides are going to enter the registration process. By then we ought to have gathered enough know-how for a systematic risk assessment.»

FROM THE CRADLE TO THE GRAVE

Only just produced, bound within another material, then worn down by use, washed out by the rain, disseminated by the hands of the weather and finally burnt at a waste disposal site: a synthetic nanomaterial's life cycle essentially determines what kind of risk it poses.

In suntan lotion, risks appear at the time the product is being used, in electronic products they appear at the stage of recycling: depending on the material and the type of use it is put to, compounds containing nanomaterials will release them sooner or later into the environment, the air, the water, sediments or soil. Quantifying them is not possible yet: no methods have been yet established that are capable of detecting trace concentrations of synthetic nanomaterials in environmental samples.

However, *Bernd Nowack* from the Department of Technology and Society at Empa in St. Gallen, is able to compute this: using his computer models he quantifies the most important mass flows of a diverse range of nanoparticles in the environment, compares them with eco-toxicological test results and legal limits and thus arrives at a sound basis for evaluating risk: «This data provides us with added certainty about environmental concentrations and enable us to base the discussions about potential risks on a more robust foundation», he says.

The estimates that Bernd Nowack and his research team produce on the basis of their models are the best data sets available at present on the mass flows of nanosilver, nanozinc, nano-titanium dioxide, fullerenes and carbon nanotubes in the environment. The model used is a dynamic one: it takes into consideration the growing use of nanomaterials in industry, during production, use and disposal and it also includes various types of applications. The group has also simulated how nanomaterials behave when they enter aquatic environments. Here, the most significant process proved to be the nanoparticles' tendency to bind to natural solids floating in the water.

Bernd Nowack did not carry out a risk assessment with his new model. A comparison with earlier work, however, prompts him to conclude, «based on current production quantities, nanoparticles do not pose an environmental problem». With one exception: in the case of nano-zinc oxide – primarily used in cosmetics and pharmaceuticals – environmental concentrations are approaching critical thresholds: «This material should be top of the list for future eco-toxicological studies and investigations», concludes Nowack.

Dangerously obstinate

As light as a feather and yet stronger than steel: carbon nanotubes are the shooting stars amongst nanomaterials. Due to their electronic and mechanical characteristics they are used as filler material and are embedded inside other materials whose characteristics they enhance: at the same token, these tiny tubes have the aura of the perilous. Again and again, the fear that these fibrous nanomaterials may turn out to be just as dangerous to health as certain asbestos fibres resurfaces – fears such as these are harboured not least by insurance companies. «No other nanomaterial has been the subject of as much research over the past two decades», explains Empa researcher *Jing Wang,* «there are lots of toxicity studies and there are lots of indications that rigid nanotubes from a certain length upwards may indeed cause problems if inhaled.»

Jing Wang was interested in the question whether carbon nanotubes could be set free again through abrasion, wear-and-tear or breakage of the composite material, in which quantities this would happen and how dangerous it would be for human health. To find this out, he and his team produced their very own composite material in the laboratory, subjected it to an ageing and wear-and-tear process which simulated normal material wear or material failure, and examined the resulting abrasion dust. They found carbon nanotubes in the abraded particles in a variety of shapes: still partially embedded in the material, partially protruding out from it – something which had never been evidenced before – totally freestanding and therefore potentially dangerous, since they are susceptible of entering the lungs in this form. An analysis method developed especially for this study enabled Jing Wang and his team to determine

Hans-Peter Kohler
Eawag Dubendorf

the amount of freestanding carbon nanotubes. The finding does not cause any reason for alarm: its content within the abrasion dust did not exceed more than 0.0004 percent of the carbon nanotubes originally embedded inside the material. A toxicity test carried out with *in vitro* lung cell cultures did not identify any acutely damaging effect. Potential long-term effects were, however, not investigated: «It would certainly be premature to draw any conclusions from this for regulatory purposes», says Wang. Nonetheless, his findings allow lessons to be learnt for the production of nanocomposite materials. Carbon nanotubes should be embedded in the matrix in such a strong way that any potential risks are cut down to a minimum right from the outset.

In the end poorly digestible

The last phase in the life of nanoparticles is what concerns *Hans-Peter Kohler* from Eawag in Dubendorf. He developed an analytical method to examine how quickly carbon-containing nanomaterials will degrade in biological systems, or put in simpler terms, how quickly enzymes can digest these particles and convert them back into their mineral components. Whereas previous studies assumed that this decomposition process took place very quickly in the environment, his work shows half-life periods of several decades.

So, between the predicted 8 days and Kohler's findings of 80 years lies a definite difference: carbon nanotubes have in reality a much greater longevity than previously believed. For future regulatory measures and production standards, this constitutes vital information, especially since his findings gathered from *in vitro* methods represent a best-case scenario, according to Kohler: in nature, the nanoparticles might be even more bio-resistant than shown here. However, the analytical methods with which this could be tested, do not currently exist. Hans-Peter Kohler therefore believes that investing more research funds into the area of nano-environmental analytics would be a lucrative step for Switzerland in the long run.

THE DEVIL IS IN THE DETAIL

Actually, and to put it bluntly, the only thing that different nanomaterials have in common is the prefix «nano». And this, in actual fact, does no more than give us an indication as to the dimension that we are dealing with here: «nano» in scientific terms means «a billionth of a metre». Of course, things are not quite this simple: the small size has an impact on the physical-chemical properties of nanoparticles and results in them reacting differently than larger particles of exactly the same chemical composition when interacting with biological systems – but they do not all always «react differently in identical ways»! Physicist Martin Frenz from the University of Berne explains: «How a nanoparticle affects a cell is heavily dependent on its surface composition, on its loading and size, the particle concentration, the duration of the exposure and other factors. This makes it impossible to draw direct conclusions from one nanoparticle to another.»

Blanket responses therefore do not do these nanoparticle justice and risk assessments must be made in a much more differentiated manner: «Frequently, size is not all relevant for these problematics», says Empa researcher Bernd Nowack, «Nanosilver for instance has been used for over 120 years for its antibacterial properties, and similarly, silica is used in medicine since World War II. And some substances have simply slid into the 'nanomaterial' category in the wake of the new definition». An important aim of NRP 64 was therefore to identify where in actual fact a nano-specific problem did exist, and where by consequence – as far as production, use and regulations are concerned, a 'nano-specific answer' is imperative.

Better safe than sorry

Complicated? It is going to get even worse. Behind different nanoparticles and nanomaterials are different production and processing methods. This makes it necessary to characterise each nanomaterial individually, which in turn necessitates recognised criteria, standardised test methods and analytical procedures. But as long as these are not available, any literature published in the field of nano-research will not necessarily provide reliable know-how.

According to many Swiss nano-researchers, a number of shortcomings still exist in the characterisation, analysis and standard testing of nanomaterials. In order to remove them, strenuous research work is still needed. This type of work yields, at first sight, unimpressive and dull results and is therefore unlikely to get funded at all. Different NRP 64 projects indicate how short-sighted such a strategy is and have, thanks to innovative measuring devices, new analytical tools and models, contributed immensely towards closing this gap – and have also brought home the realisation that further efforts are vitally important in this area: «First and foremost, internationally recognised standard methods ought to be published and reference material ought to be made available. Without this knowledge, millions if not billions of Swiss francs will lie idle, because the step towards industrial application cannot be taken» says for example Reto Luginbühl from the Robert Mathys Foundation in Bettlach. This is particularly true in medicine: « Nanomedicine opens up enormous opportunities. But if we really want to bring nanomedical applications to clinical settings one day, then we must take the time and deploy the required resources to carry out thorough risk analyses», says Beatrice Beck Schimmer from the University Hospital Zurich. Regulatory conditions remain equally futile as long as no reliable test equipment exists that can prove nanomaterial existence: «Here, last but not least, politicians need to act», believes Barbara Rothen-Rutishauser from the Adolphe Merkle Institute in Freiburg.

A noteworthy approach to close such gaps is the EU project NANoREG, which dealt with the safety aspects of synthetic nanomaterials and which compiled the know-how for regulatory purposes. Through the NRP 64 programme, and in collaboration with the relevant federal offices, Switzerland pro-actively participated

Caroline Maake
University of Zurich

in this project that was able to answer many of the questions that concerned safety issues for society, industry and national authorities.

The dose makes the toxin

A few old truths stood the test of time and also hold true in the new world of nanoparticles. For instance the realisation of the legendary Paracelsus that a toxic substance in small doses can be harmless, while the excessive consumption of harmless substances can be toxic. Nonetheless, quantifying nanoparticles in the environment proves difficult; *in vitro* studies frequently use doses that are too high, so that any inference thereof regarding «real life» have only limited validity. For this reason intensive efforts are being made to adjust the doses used in research to those which one would likely be exposed to in real, daily life – for example at the workplace.

Add to this a further point: to evaluate the potential risks posed by nanomaterials for human health or the environment, the following formula applies: «Risk = Dose x Exposure». So what is important is not just the dose, but also crucial is how long a microorganism is exposed to a certain substance within an ecosystem, or how large the concentration of nanoparticles that accumulates within a biological systems is, knowing that the nanoparticles will then accumulate and be concentrated along the food chain (bio-accumulation). Long-term studies do, for the most part, not exist at present, and this with regard to duration of exposure, but also for the time after exposure. Investigating these factors would be particularly important: it would show whether or not biological systems are able to recover from an onslaught of nanoparticles.

It goes without saying that a five-year research programme cannot answer such questions. Asked what message she had for the authorities and politicians, physician Caroline Maake from the University of Zurich, put it in a nutshell: «Just keep going!»

A WORTHY CAUSE

«We have learnt a wealth of new information about nanomaterials in these past years», summarises Martin Frenz from the University of Berne the NRP 64 Programme. «The carpet had been rolled out», he says further and with this he means the annual meetings, the reporting and the numerous opportunities for collaboration and for exchanging ideas that were made possible by this National Research Programme: «Again and again this resulted in the approach and findings of one group prompting new perspectives and solutions in another group, which would have never been discovered otherwise.»

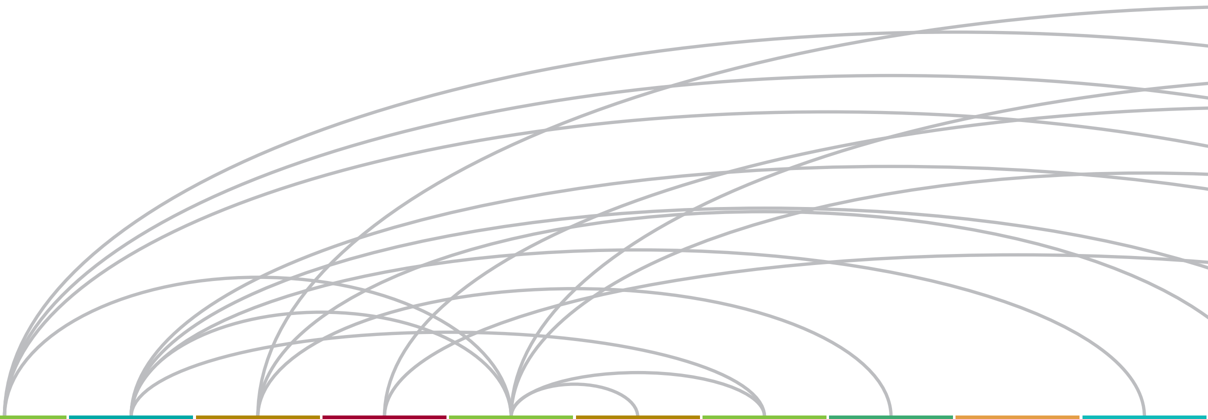
Taking a peek across the interdisciplinary garden fence is not always possible in general in research – even if at times one would not have to wander too far afield: Christoph Weder from the Adolphe Merkle Institute for instance, established within the scope of NRP 64 a close cooperation with Barbara Rothen-Rutishauser, a researcher he had not met before, but who also works in the same institution, albeit in a different field. For him, too, one of the best features resulting from national research programmes is the fact that it mobilises forces and creates new networks: «The nanocommunity, that came about through the NRP 64 programme will continue to exist long after the programme is finished» he asserts. ETH professor Jing Wang, who collaborated closely with Empa researcher Peter Wick for his research of environmental risks posed by carbon nanotubes, expressed his appreciation for the impressive insights he gained into biological interactions that were utterly knew to him and which have already sparked new research projects. «Cross fertilisation» is how Michael Zimmermann from the ETH Zurich calls this, «without a shadow of a doubt, an enormous plus of the NRP.» Ralf Kaegi from the Eawag in Dubendorf emphasises another aspect: «I'm impressed by how much bigger the sum of the whole is in such a research consortium compared to what would have been achieved if the projects had been undertaken independently», he says. «And all this thanks to a lean organisation, minimal bureaucracy and efficient programme coordination, devoid of frictions and on a rather modest budget, as compared with other EU initiatives.»

As mentioned in the tender documents, National research programmes are intended to produce sound scientific contributions «to solving present day problems of national importance».

However, they tend to do a lot more than this. Besides the cooperation and interdisciplinary interlinking that they enable, there is also the positive effect they have in fostering junior researchers. Many research groups stress this point, in particular the interdisciplinary training of young scientists, where industry representatives were invited and where important aspects of know-how and technology transfer were addressed. «The very special scientific environment that is part and parcel of such programmes, is immensely exciting for doctoral students and young researchers», says Hanspeter Nägeli from the University of Zurich, «and the more doctoral candidates and postdocs such a NRP can motivate into pursuing a career in science, the greater the sustainability of the programme.» Beatrice Beck Schimmer from the University Hospital Zurich stresses the importance of well-trained young talent, especially in this highly complex area of synthetic nanoparticles. She believes: «Uses for synthetic nanomaterials are only going to get a foothold in medicine if we approach this with the utmost care, looking in great detail at the whole cycle of these particles with all their possible side effects. This takes time and a sizeable amount of manpower.»

One small downside was finally mentioned by Bernd Nowack from Empa in St. Gallen. Despite his considering the findings of the NRP 64 as being of first-class quality in a global context, he believes Switzerland has missed the opportunity of taking up pole position in the field of nanotechnology: «England and the USA are ahead of us», he states, «the NRP 64 came a little too late.»

Cooperation networks



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- → European Cooperation in Science and Technology (COST ES 1205), D

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- → Netherlands National Institute for Public Health and the Environment (RIVM),NL
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- → Federal Institute for Materials Research and Testing (BAM), DE
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- → University of North Carolina, USA
- → University of Washington, USA
- → University of Miami, USA
- → University of British Columbia (UBC), CDN
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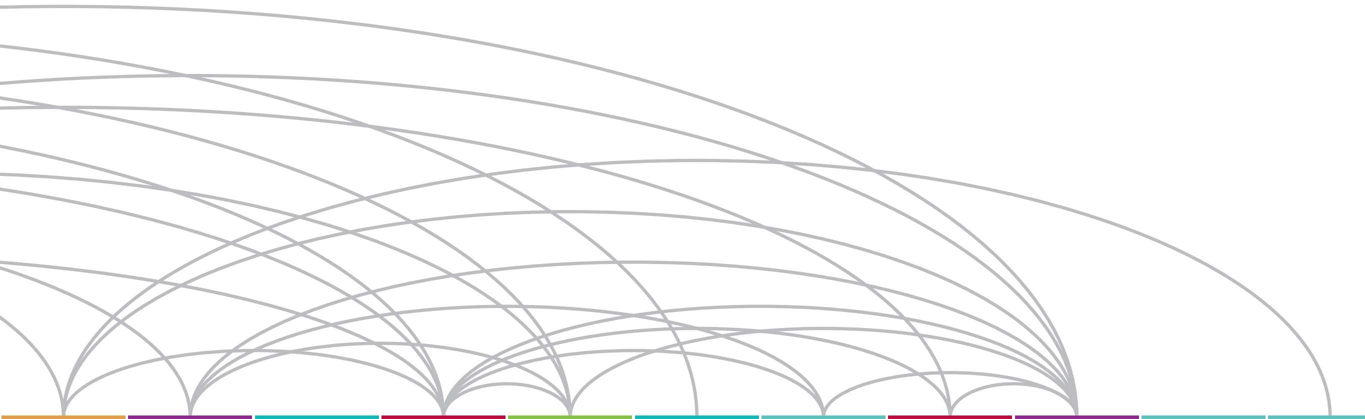
- → Institut Universitaire Romand de Santé au Travail (IST), CH
- → National Institute of Chemical Physics and Biophysics, Tallin, EST

Illustration of the interlinking of both the research groups amongst one another and of research groups and cooperation partners



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- → Berne University Hospital, CH
- → Laboratoire d'Etude des Résidus et Contaminant dans les Aliments (LABERCA), F
- → Federal Institute for Risk Research, Berlin, DE
- → RIKILT-Institute of Food Safety, NL
- → Queen's University, Belfast, GB/IR
- → Food & Environmental Research Agency, York, GB/IR
- → Karolinska Institute, S
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- → Clinical Research Center, Lausanne University Hospital (CHUV), CH
- → RIKILT- Institute of Food Safety, NL
- → National Institute for Occupational Safety and Health (NIOSH), USA

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- → School of Materials, University of Manchester, GB/IR
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- → National Institute of Stanard and Testing (NIST), USA
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- → Laboratory of Toxicology, Institute of Food, Nutrition and Health ETH Zurich, CH
- → Safety and Environmental Technology Group HCI, ETH Zurich, CH
- → Department of Pharmaceutical Sciences, University of Basel, CH
- → Swiss Centre for Applied Human Toxicology University of Basel, CH
- → Institute of Biochemistry and Molecular Medicine, University of Bern, CH
- → Federal Office of Public Health (FOPH), CH
- → Austrian Institute of Technology Vienna, A
- → National Institute of Standard and Technology NIST, USA,
- → Department of Obstetrics and Gynecology University of Texas, USA

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ALL'S (almost) WELL THAT ENDS WELL

Peter Gehr, professor emeritus of Anatomy and Histology at the University of Berne, has, as President of the Steering Committee, accompanied the NRP 64 closely throughout its duration. Time to make an assessment.

23 research groups have grappled intensively and for a number of years with the opportunities and risks harboured by synthetic nanomaterials. Which findings did impress you the most?

I almost don't know where to start! The artificial cartilage, the possibility to repair blood vessels inside the brain or the unexpected bioresistance of carbon nanotubes certainly are some of the highlights. But also, measuring cell reaction to nanoparticle exposure must count as one, or the realisation that wastewater treatment in general is efficient or that plant and animal cells react differently to silver ions. Equally worth a mention is that certain nanoparticles pass through the placenta or the possibility to cleanse blood, control the immune system or mimic viruses in order to smuggle medication into cells. I could continue with this list, but in general this much can be said: all this new knowledge will be helping Switzerland to further expand on its strengths in the development of innovative nanomaterials and in assessing their risks, so as to position itself right at the top of international nanoscience.

Where do important knowledge gaps still exist?

We do know a lot more, but there is still so much more to discover. On the one hand we have gained new insights about new technologies, equipment and application possibilities, but on the other hand we have found out about mechanisms of action, i.e. about how nanoparticles interact with biological systems and what this means. We are still in need of long-term studies, i.e. studies that show the effects that long-term nanoparticle exposure has on the body and the environment. We also know very little about what happens after such an exposure has taken place: does the defensive reaction of a biological system subside again – which would mean that «it calms down again» or does it continue? The knowledge gap regarding indirect exposure through bioaccumulation is massive: far too little is known as yet as to how nanoparticles accumulate in the environment and in organisms and how they are then passed along the food chain.

New nanomaterials promise to open up phenomenal possibilities in many technical areas. Is the NRP 64 able to confirm the expectations that industry and society hold?

I think so. Let us just look at the possibility of using nanoparticles for an efficient and reliable transport of medication, or to reliably measure the oxidative stress of living cells or to produce much smaller yet more efficient batteries. The fact that we are today better able to classify nanoparticles and are more competent at assessing their risks is going to pave the way towards a large number of promising innovations.

The consultation group that stood at the ready behind the scenes throughout the entire duration of NRP 64 in order to immediately inform the public in the event of any alarming findings never had to spring into action. Does this mean that the handling of new nanomaterials can be considered to be safe in general?

Fundamentally, no significant problems were discovered – on the other hand, indications of potential risks emerged that must be verified and investigated further. The lungs remain the main point of entry into the body for nanoparticles. But what exactly does it mean when inhaled nanoparticles enter the blood via lung tissue, from whence they are transported to all the organs, if under certain circumstances they overcome the blood-brain barrier or pass via the placenta from the maternal blood circulation into the foetal blood circulation? The human body has a number of many other important tissue barriers between blood and organ-specific tissue, which may also allow penetration. This area requires further research. What happens, for instance,

when nanoparticles enter the digestive tract in the form of food additives? Are they able to enter the tissues there and if so, what are the effects?

We often hear about nanoparticles being called the new asbestos. Do we now know more about this?

First of all, it is important to clarify that not all asbestos fibres present a hazard: only rigid needle-shaped fibres whose diameter is on the nanoscale and whose length is on the micrometre dimension can damage the lungs and can even cause lung cancer. Carbon nanotubes, which resemble such asbestos fibres in terms of structure and dimension, may trigger the same reactions as could be shown in *ex-vivo* and animal tests. We should stress though, that this potential danger only exists during production and possibly during disposal, when nanoparticles enter the atmosphere from where they can be inhaled. Using a bicycle with a frame that is made stronger by using carbon nanotubes does consequently not pose a health risk.

Can lessons be learnt from the NRP 64 for the production, the use and the disposal of synthetic nanoparticles?

If there is a generally valid conclusion to be drawn from it then it might be this: NRP 64 shows that each new nanomaterial and each new application always necessitates as a matter of principle a new risk analysis.

The NRP 64 was named «Opportunities and Risks of Nanomaterials». But which of the two wins?

Without a doubt the opportunities. Synthetic nanomaterials have a scientific, an industrial and a medical-clinical potential that is second to none. However, market-ready applications are only possible when we are on safe ground, this means we must always keep a keen eye on weighing up the risks. Credit must be given to the NRP 64 for having enabled us to make this great stride forwards. We now know where we need further scientific foundations and where further research potential exists. And we are able to declare that the precautionary matrix put together by the Federal Office of Public Health, which allows industry and trade to weigh up the health and environmental risks of handling nanoproducts, is fit for its purpose at present, and that no further regulations in the sense of restricting application, are needed at present.

NRP 64 : THE 23 PROJECTS

Biomedical applications

Carbon coated nanomagnets and their in vivo life cycle

Prof. Beatrice Beck Schimmer

Nanoparticles in biodegradable implants: distribution and effects in brain tissue

Prof. Martin Frenz

Risk analysis of inhaled nanoparticles by in vitro technology

Prof. Marianne Geiser Kamber

Biomimetic nanofibre reinforced bone substitute composites

Dr. Reto Luginbühl

Nanopharmaceuticals against chronic inflammatory bowel disease

Prof. Caroline Maake

Analysis and fate of nanoparticles in the lung and expected biological effects

Dr. Michael Riediker

Biomedical nanoparticles as immune-modulators

Prof. Barbara Rothen-Rutishauser

Novel nanoparticles for efficient and safe drug delivery

Prof. Francesco Stellacci

Nanoparticle transport across the human placenta

Dr. Peter Wick

Environment

Silver nanoparticle effects at the food web and ecosystem level

Dr. Renata Behra

Effects of nanoparticles on soil microbes and crops

Dr. Thomas Daniel Bucheli

Behaviour of silver nanoparticles in a wastewater treatment plant

Dr. Ralf Kaegi

Biotransformation of carbon-based nanomaterials (BioCarb)

Dr. Hans-Peter Kohler

Non-invasive continuous monitoring of the interaction between nanoparticles and aquatic microorganisms

Prof. Olivier Martin

Modelling of nanomaterials in the environment

Prof. Bernd Nowack

Interaction of metal nanoparticles with aquatic organisms

Prof. Kristin Schirmer

Food and food packaging

Risk analysis of nanoparticles in food

Prof. Hanspeter Nägeli

Gastrointestinal exposure to nanoscale iron compounds in foods

Prof. Michael Zimmermann

Energy

Opportunities and risks of nanoscale electrode materials for lithium-ion batteries

Prof. Katharina M. Fromm

Safety of nanomaterials in lithium-ion batteries

Prof. Vanessa Wood

Construction materials

Evaluation platform for safety and environmental risks of CNT reinforced nanocomposites

Prof. Jing Wang

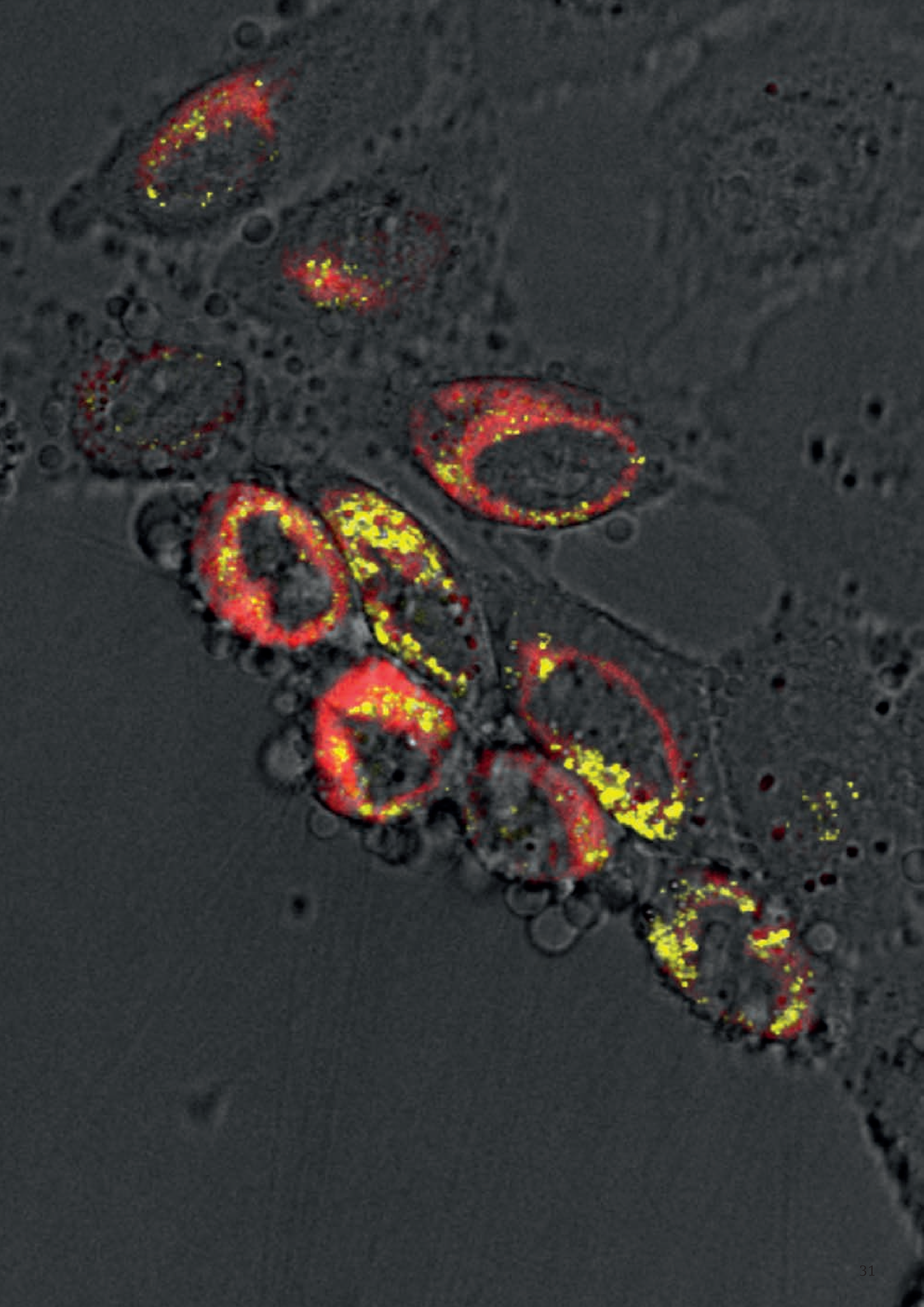
Assessment of the effectiveness and environmental risk of nano copper based wood preservatives

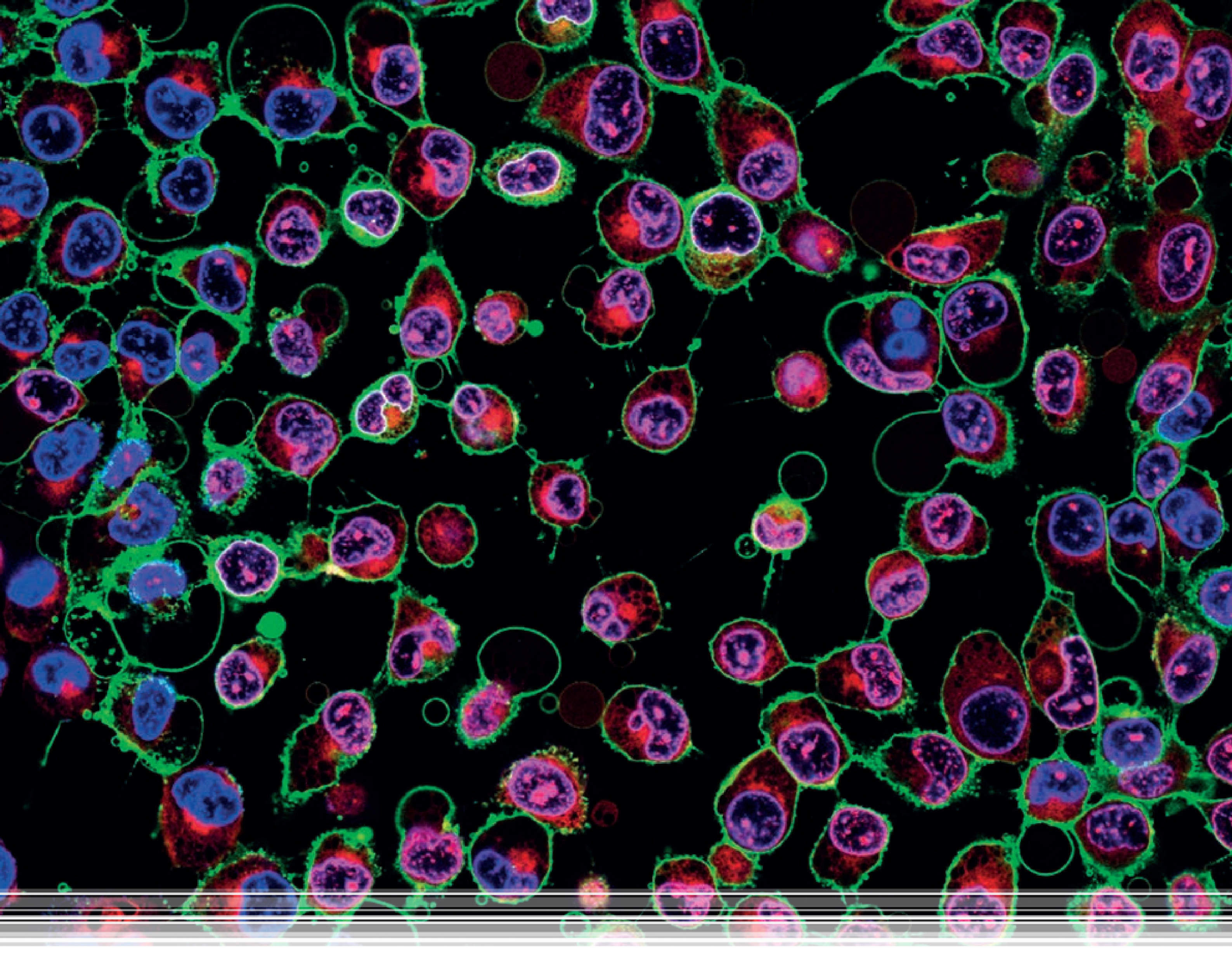
Dr. Peter Wick

Cellulose-based nanocomposites as novel building materials

Prof. Christoph Weder

Dying cancer cells after treatment with nanopharmaceuticals.





Opportunities and Risks of Nanomaterials
National Research Programme NRP 64

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For more information: www.nrp64.ch

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