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Carbon nanotubes – Part II: Risks and Regulations

Summary

Carbon nanotubes (CNTs) can be inhaled and thus deposited in the lungs. Studies have shown that specific CNTs, namely those that are long (10-20 μm), thin (5-10 nm), needle-shaped and non-soluble (biopersistent), can promote the formation of lung diseases and show behaviour similar to that of asbestos fibres. Short or long fibres that are not needle-shaped will not, however, induce inflammatory changes, no more than a single carbon particle would. Comprehensive life-cycle analyses regarding the potential environmental benefits arising from the use of CNTs (such as resource savings owing to more light-weight materials) are not available to date. At present, the production of CNTs still requires a high energy input, which offsets any potential environmental benefits. Their high reactivity and ability to transport other substances raises concerns about a possible ecotoxicity of CNTs. The data available are still restricted in scope, and the discussion of results is controversial. Given the lack of reliable data on exposure, an adequate assessment of health and/or environmental risks is not possible for the time being.

At present, specific regulations for CNTs or other nanomaterials exist neither in the laws governing chemicals nor in regulations for occupational health and safety. Hence, the relevant authorities recommend that the precautionary principle should be applied and measures taken to avoid exposure or keep it as low as possible.

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Introduction

The use of carbon nanotubes (CNTs) in engineering or medicine raises great hopes for innovative applications and, consequently, considerable economic potential (also see dossier no. 022en). Conversely, there are justified concerns that the use of CNTs could have negative impacts on human health and the ecosystem. Some of these health impacts can be avoided by avoiding specific CNTs. Difficulties also exist with a view to detection procedures and measurement methods. At present, there is no reliable technology to conduct measurements of CNTs concentrations and their analysis at the same time, to be applied for instance in the workplace. This statement is, however, true for most hazardous substances. This dossier provides an overview of potential risks CNTs might pose for health and environment, as well as information about ongoing regulation activities.

Toxicity

In the first decade after the discovery of CNTs[1], potential negative health impacts were not studied closely – mostly due to the fact that the production methods available at the time only allowed researchers to produce CNTs at laboratory scale and high cost[2]. Around the turn of the millennium, when new methods (chemical vapour deposition at reduced pressure) made it possible to produce larger quantities of CNTs on an industrial scale, the health impact of this material was increasingly studied through toxicological investigations.

It was the similarity of CNTs to asbestos fibres regarding their shape and persistency that triggered first health warnings, for it is known that the handling of various asbestos materials can elicit inflammatory reactions in the lung that may result in lung cancer and or mesothelioma (connective-tissue tumours of the pleura or protective lining around the lung). The latter are not necessarily malignant. They develop when macrophages (phagocytic cell) try to absorb the needle-shaped asbestos fibres but fail to do so because these are too long. This gives rise to the development of so-called giant cells produced by several cells fusing into one in order to be able to ingest the fibres. The chronic activation of these giant cells (a permanent attempt to digest the fibres) leads to nodular new tissue formation, so-called granuloma, which may develop into a mesothelioma with a long latency period of 30 to 40 years. This may be due to the fact that the fibres move very slowly from the inside of the lung to the peritoneum[3] and cannot be broken down by the body during this time.

It must be underlined that CNTs exist in great diversity, and their biological impact depends on their shape. It is assumed that CNTs that look like asbestos fibres will also behave similarly to asbestos in the lung. In order to verify that assumption, most investigations involve inhalation studies on animals (in vivo, mostly using rats or mice). The animals are either exposed to CNTs and inhale them through the nose, or the fibres are applied directly to the lung or thorax (by instillation).

One research team, for instance, found that intraperitoneal injection of long (ca. 20 μm) needle-shaped nanotubes resulted in chronic inflammation, but there was little or no such effect caused by short needle-shaped, or by curved and long and curved nanotubes. Since these nanotubes resemble asbestos fibres as regards their properties (shape, length and solubility), a comparable response to exposure was discussed. The study deliberately used nanotubes similar in shape and length to asbestos fibres, as well as differently shaped ones for comparison. The results show that high concentrations (50 μg/per mouse, with the weight of a mouse being ca. 20 g) and long and needle-shaped nanotubes can elicit chronic inflammation (granuloma)[4], whereas short and/or curved nanotubes do not. A similar study was conducted with long and thick SWCNTs (single-walled CNTs) and MWCNTs (multi-walled CNTs) in mice. The strongest response was elicited by long and rigid as well as thick and rigid MWCNTs, whereas short and thin, as well as flexible SWCNTs hardly triggered inflammation[5].

It is also known that the surface properties of nanoparticles can have an influence on their biological effectiveness. It was shown, for instance, that water-soluble SWCNTs injected into mice (up to 400 µg/mouse) are quickly excreted through the kidneys with a half-life of three hours[6]. Another research group presented similar results, whereby chemically altered (hydroxylated) SWCNTs were quickly distributed in the body regardless of the form of application (injected intravenously, subcutaneously or into the abdominal cavity) and were eliminated just as quickly through urine[7]. This means that non-biopersistent CNTs can easily be processed by the body.

After a single aspiration exposure of mice to highly concentrated (30 mg/m^3) MWCNTs (0.5 to 50 µm), it was shown that the particles penetrate to the subpleural region, i.e. under the protective lining of the thoracic cavity. At lower concentrations (1 mg/m^3) such effects were not observed[8]. Another study[9] corroborated these results and found that aspired MWCNTs (ca. 4 µm, 10-80 µg per mouse) reached the pleura after 56 days and elicited an inflammatory response there. These insights are of major significance, since pathogenic fibres (such as asbestos) are known to induce diseases such as mesothelioma particularly in the pleural cavity.

It must be noted, however, that the concentrations used in animal testing are extremely high in order to elucidate the biological response mechanisms and, thus, the impact of nanoparticles. In one of the above studies, each of the mice inhaled 30 mg MWCNTs per m^3 air. For an average human being with a body weight of 70 kg this would correspond to approx. 100 g per m^3 air. As CNTs are very light-weight, 100 g would have a volume of almost 700 ml[10]. Hence, 30 mg of CNTs per cubic metre of air is a very large amount for a mouse that weighs ca. 20 g. While such tests are very important, the data are still preliminary and the results only show short-term effects. Long-term studies with CNT exposure under realistic conditions are still lacking.

How will CNTs behave when they enter the body through the mouth? There is only one study on the acute toxicity of orally ingested SWCNTs[11]. In the study, mice were administered single doses of 1000 mg/kg body weight of three types of SWCNTs: SWCNTs (1 nm × 1-2 µm, 25 % Fe, metal impurities), purified SWCNTs (1 nm × 1-2 µm, < 4 % Fe) and ultra-short SWCNTs (1 nm × 20-80 nm, < 1.5 % Fe). Despite the high concentrations and the different CNT types, no toxic effect was observed after 14 days.

In-vitro studies (experiments on cell cultures) also demonstrate potential risks and the mode of action of substances such as CNTs, but do not realistically reflect the in-vivo situation. There is a large number of in-vitro studies, using different cell systems, CNTs, concentrations and functionalization (surface modifications), in order to reveal mechanisms or study changes in the genetic substance, i.e. the genotoxic potential of CNTs. Standard and modified in-vitro tests were also carried out to investigate possible positive effects and their mechanisms. Genotoxic effects can take either a primary route by direct contact with the DNA or a secondary route through inflammatory reactions such as the formation of reactive oxygen species (ROS) (see [12]). It has been shown that both are possible, depending on the purity of CNTs administered. The production of CNTs gives rise to metal by-products that may induce or increase an effect. As contradictory results have been described depending on the biological system, the genotoxic potential of CNTs in vitro has not been conclusively determined to date (for comprehensive overviews see [5; 13-15]).

Because of their very small mass and dimensions, CNTs can remain suspended in ambient air for a long time and, when inhaled, reach even the tiniest ramifications of the lungs. There is very little information about whether CNTs can be degraded in a biological environment – that is to say under natural conditions. A research team described that SWCNTs can be degraded (in vitro) with the help of natural enzymes[16]. It remains to be clarified whether and how fast CNTs degrade, since this would also supply important information about their bio-availability. As CNTs can have pathological effects over a long term, these data are of great significance.

An overview published in 2010[17] provides a summary assessment on CNT toxicity. The study particularly mentions the risks for people with occupational exposure to CNTs and confirmed the generally agreed hypothesis that very specific types of CNTs, namely long, thin, needle-shaped, and biopersistent CNTs, can have pathological effects comparable to those triggered by asbestos fibres.

Environmental Impact

Processes and products that involve nanotechnology harbour some promise, including that of environmental benefits, for instance by saving raw materials and energy. In the future, construction parts made from CNT-optimised plastics for vehicles or aircraft may decrease fuel consumption because of their lighter weight. CNTs may also improve the thermal and mechanical properties of plastics and make them increasingly competitive with metals[18]. Existing studies, however, assess environmental benefits mainly in qualitative terms, and there are only a few isolated life-cycle analyses (LCAs). What is usually lacking in descriptions of the environmental benefits of nanotechnology products and applications are analyses and assessments of the resource and energy input required for their production. Environmental organisations are concerned that the benefits claimed may be exaggerated and warn that the new technology may even involve higher energy-related and environmental costs[18]. CNT production does indeed require a great deal of energy – first estimates speak of 0.1 to 1.0 TJ (terajoule) per kilogramme[19]. One TJ corresponds approximately to the amount of energy supplied by 167 barrels of oil (ca. 26550 litres)[19]. This would make CNTs one of the most energy-intensive materials known. Production methods differ, however, with respect to their energy consumption,

Forms of carbon – name of substance	EC No.	CAS No.
Carbon	231-153-3	7440-44-0
Carbon Black	215-609-9	1330-86-4
Graphite	231-955-3	7782-42-5
Fullerene C_{60}	–	99685-96-8
CNTs	–	–

Table 1: EC and CAS (Chemical Abstracts Service) registration numbers of carbon-based nano-scale materials

Table 2: Selected countries and their CNT regulations

Country	Regulations on nanomaterials – and specifically on CNTs	Sources
EU	• No nano-specific requirements at present	33; 34
	• As of the entry into force of REACH in 2008, the precautionary principle has had to be applied and all chemicals exceeding 1 JT require registration with the relevant EU authority (ECHA) prior to use	35
	• In principle, "chemical equivalents" of substances already registered do not require re-registration	
	Demands for changes	
	• EU-Parliament demands that all nanomaterials be treated as new substances, as well as an overview of all nanomaterials in use and regulatory evaluation by the EU Commission before 2012	26
	First new requirements	
	• The exemption status of carbon was removed in 2008 with an explicit reference to nano-risks	
	• At international level, Fullerenes C60 have already been recognised as having specific properties which merit separate CAS registration	
	• This is not yet the case for CNTs	
USA	• Previously: voluntary submission of information on nano-substances; only few companies responded	36; 37
	New regulation	
	• Since 2010, SWCNTs and MWCNTs have been subject to strict notification requirements within the context of the Toxical Substances Control Act. Their manufacture, import or use (also as a continuation of ongoing activities) requires notification	
Australia	• Previously: voluntary submission of information on nano-substances	38
	New regulation	
	• SWCNTs and MWCNTs are new chemicals	
	• Pre-import authorisation required under the Industrial Chemicals Notification & Assessment Act 1989	
	• Details of the new regulation will be decided in 2011	
Japan	• Up until now: discussion rounds and considerations as well as recommendations on CNT limits for occupational exposure	38

which leads experts to expect that technological progress and the development in production processes will lower the energy input required.

Their high reactivity and ability to transport other substances has raised concerns about a possible ecotoxicity of CNTs. The data available are still restricted in scope, and the discussion of results is controversial. Rainbow trout *(oncorhynchus mykiss)*, for instance, were exposed to high SWCNT concentrations (0.1; 0.25 or 0.5 mg per litre of water) for up to ten days. After this period, the fish showed pathological modifications of their gills as a function of the dosage[20]. Larvae of the African clawed frog *(Xenopus laevis)* were exposed to a concentration of 10 to 500 mg of double-walled CNTs per litre of water. Acute toxicity was found in all concentrations giving rise to a blocking of the gills and/or digestive tract. Under the microscope, the respective organs showed black CNT agglomerations[21]. To date, an analysis of marine organisms or ecosystems has not been conducted[22], but it is known that a number of methodological problems exist in determining the toxicological profile of CNTs. For examinations, CNTs need to be dissolved in water. Due to their poor solubility, scientist use different methods and chemical solvents which may, in turn, influence the test results. In addition, as has already been emphasised, CNTs manifest great diversity, with differences in structure, size distribution, surface chemistry and charge, agglomeration behaviour and purity. These differences have a decisive impact on their reactivity and, thus, also on their toxicity. Another critical issue is the often unrealistically high dosages used in ecotoxicity tests. Given their properties, CNTs would be expected to agglomerate (bunch together) and sediment (settle) in the water. In ecotoxicity tests, however, the surfaces of CNTs are often functionalised (for instance with chemical compounds or by coating), which may increase their stability in water systems and influence both their environmental behaviour and their toxicity[22].

The identification of potential environmental risks indispensably requires data on exposure, which do not exist for the time being. An estimate for 2007/08 assumes a worldwide production volume of not more than 500 t[23]. A lack of information on products containing CNTs makes estimates of that kind extremely difficult. Given the fact that CNTs in consumer products are mainly incorporated in a substrate (e.g. plastics), the authors of that study see the probability of a possible release into the environment as being less during its service life than during disposal by waste incineration. As the combustion temperatures of incinerators are higher than the ignition temperature of CNTs, they should theoretically burn up completely. It is still possible to envisage scenarios, however, where CNTs would survive the incineration process. In such a case, estimates say that about 0.1 % of the total quantity of CNTs will not be captured by filters and might be released into the environment. Another study assesses current environmental concentrations of CNTs in Europe and the USA as too little to constitute any risk[24].

Regulatory Issues and Health and Safety at the Workplace

In the European Union, nanomaterials are covered by the REACH (Registration, Evaluation and Authorisation of Chemicals) regime for chemicals. REACH has a central database that registers all chemicals produced or imported in the EU in quantities of one tonne per year or more per manufacturer or importer. A chemical safety report needs to be submitted only if the quantity is ten tonnes or more. REACH has often been criticised for failing to take sufficient account of nano-specific properties[25]. In principle, substances that seem to be of particular concern can be subject to restrictions under Art. 57 of REACH. Before the European Chemicals Agency (ECHA) can apply such restrictions, however, a comprehensive procedure of comments and consultation must be conducted and the approval of the Member State Committee sought. In the summer of 2010, ECHA published a new Candidate List of Substances of Very High Concern (SVHC) with almost forty substances – none of them a nanomaterial. Owing to the high quantity thresholds of the regime – a tonne per year or more for registration and ten tonnes per year or more for the mandatory submission of a chemical safety report – many nano-scale chemicals are not subject to any registration.

Chemicals legislation in the EU and in the USA (TSCA; Toxic Substances Control Act) uses as its defining criterion exclusively the "molecular identity" of a substance, i.e. its chemical composition, but does not take the particle size or nano-specific properties into account. That this is a problem has become particularly obvious in the regulation of carbon-based materials. In REACH, carbon was initially considered to be of no concern ("minimum risk because of its intrinsic properties"). At the end of 2008, this exemption status was removed with an explicit reference to the nano-scale forms of carbon[26]. In addition to carbon, carbon black and graphite, C60-Fullerene was also given a separate CAS (Chemical Abstracts Service) registration number in line with international denomination standards for chemicals, since these materials were clearly different from each other despite having the same molecular identity. For CNTs, this step has not yet been taken (Table 1).

In contrast to the EU, the USA made CNTs subject to strict notification requirements within the context of the Toxic Substances Control Act in October 2010. Their manufacture, import or use (also as a continuation of ongoing activities) has to be notified to the authority, which has to decide within 90 days whether the substance may be imported or processed. The only exception is granted to CNTs firmly embedded in a matrix. (For an overview of regulations for nanomaterials – particularly CNTs – in the EU, the USA and Australia and Japan see Table 2.)

As regards health and safety at the workplace, the EU has not adopted any nano-specific regulations. The minimum requirements as laid down by the relevant EU directive[27] relate to the protection of the health and safety of workers without making explicit mention of nanomaterials. Years ago, the authority in charge of this issue in the UK – the Health and Safety Executive (HSE) – already made reference to the "10 Recommendations" concerning the application of nanotechnologies published jointly by the Royal Society and the Royal Academy of Engineering[25]. In line with these recommendations, the HSE advises precautionary measures and the avoidance of risks as far as possible. In a document from 2009, HSE viewed CNTs as "substances of very high concern". Even though detailed test results are available only for a few types of CNTs (see above), health and safety and risk-minimisation measures should be guided by the precautionary principle and apply to all types of CNT materials. To the extent that the handling of CNTs cannot be avoided entirely, a high level of protection and control needs to be ensured[28]. When the British Standards Institution (BSI) submitted a draft standard, HSE pointed out the particular difficulties involved in measuring the extremely thin and light-weight CNT materials. The BSI proposed an exposure limit of 0.01 fibres/ml, but very time-consuming investigations by electron microscope would be required to monitor this limit.

In the USA, the National Institute for Occupational Safety and Health (NIOSH) proposes an occupational exposure limit of less than 7 μg CNT per cubic metre of air. In comparison, the exposure limit fixed by the EU Occupational Safety and Health Administration (EU-OSHA) for airborne graphite dust of 5 mg/m^3 represents about one thousand times as much carbon[29]. It must be emphasised, however, that dust particles are larger and therefore heavier. The measurement method proposed by NIOSH is "method 5040" [30;31] which was developed in 1999 for ultra-fine carbon dust. In this method, air is aspirated through a quartz filter and the carbon precipitate captured by the filter is measured with a thermal-optical analyser (EGA-evolved gas analysis). The proposed exposure limit of 7 μg CNT per m^3 of air is the lowest concentration that can be accurately measured[32]. Even this concentration is considered as representing an increased risk of developing adverse respiratory health effects by NIOSH. As the definition of a useful and effective occupational exposure limit for CNT depends on data about exposure and, thus, the measuring technology, it is indispensable to promote research in this area. Until such time as measurement methods are improved, efforts should be made to keep airborne CNT to a minimum and below the defined exposure level.

Conclusions

There are indications that high concentrations of very specifically structured CNTs (needle-shaped, long, thin, biopersistent) have an adverse pulmonary effect. In order to make meaningful statements on the risk involved, the mechanisms of action and dose-effect ratio have to be clarified. To avoid potential risks, the recommendation of many publications – endorsed by this dossier – is to avoid contaminations with and, if possible, the use of pathogenic needle-shaped CNTs.

Although CNT-optimized materials promise environmental benefits through resource savings, a comprehensive life cycle analysis has yet to be conducted. Available data on CNT ecotoxicity are limited and controversial. There is also a lack of reliable information on exposure that would be required for environmental risk assessment. Neither hazardous chemicals legislation nor occupational health and safety regulations offer specific requirements for the handling of CNTs. Although CNTs, like all other chemicals, are covered by the requirements of REACH, the volume-thresholds for registration (1 JT) and the mandatory chemical safety report (10 JT) have been set at levels that may not include all CNT manufacturers. In addition, CNT-specific characteristics are not taken into account. In the field of occupational health and safety, efforts are under way at international level to fix limits for occupational airborne CNT exposure. Specific regulations have yet to be adopted. In addition, there is a significant need for research and development in the field of analytical and detection methods. In order to protect employees, the relevant authorities suggest that the precautionary principle be applied and exposure kept as low as possible.

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