What are microplastics doing in our bodies?

A knowledge agenda for microplastics and health

ZonMw

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Foreword

Questions are being raised about the rising levels of microplastic in our living environment. How is the presence of tiny plastic particles in our air, food and water affecting our health, both in the short term and long term? The short answer is 'we don't know', as we have only a limited understanding of this issue. So more research is needed. However, the social dialogue on this matter occasionally creates the impression that we already know all that we need to know. Some take our lack of knowledge to mean than there is no risk at all, while others are already raising the alarm. Current government policy and the measures being taken by the business community are still based on the general precautionary principle. There is a dire need for supporting knowledge.

One of ZonMw's core activities is to identify health issues and place them on the agenda. For this reason, I am very glad that the Dutch Ministry of Infrastructure and Water Management has requested us to undertake an exploratory survey to probe the gaps in our knowledge and to develop a knowledge agenda on the topic of microplastics and health. That knowledge agenda will provide points of reference for a dialogue about the risks involved. It will also guide the quest for more knowledge and for targeted solutions. This topic is very much in keeping with the broader social theme of environment and health, a key target for efforts to improve public health. It would be great if we were able to measure the tiniest microplastics more accurately. We'd also like to find an answer to the question of whether and – if so – how various microplastics impact human health. That would enable us to more effectively monitor and improve the quality of the living environment, while identifying and addressing any associated health impacts. Once we know which plastics are safe and which are not, we can take targeted measures and devise innovative solutions.

This exploratory survey has shown that we lack even the most basic knowledge concerning this issue. It has also identified a wide range of areas in which we can make progress. The knowledge requirements of policymakers, the business community and civil society organisations have been spotlighted in this exploratory survey. This is of key importance if the research is to generate impact. One fringe benefit of the method used is that new cross-connections have been created that are vital to the development of both knowledge and solutions. The very existence of the exploratory survey has, itself, led to a strengthening of the cooperative effort.

Dutch researchers were among the first to tackle this topic. That effort involved interdisciplinary cooperation between health researchers and environmental researchers, making them global leaders in this field. I am glad that ZonMw was able to give them a helping hand, by funding fifteen one-year projects in 2019. Other funding bodies and partners have now joined in, leading to robust cooperation within a consortium of international partners. We are still at the threshold of a very protracted process, yet this encouraging beginning has provided an excellent launch pad. Many questions remain to be answered, and this agenda points the way to potential follow-up actions.

I would like to thank everyone involved in this exploratory survey for their extraordinary commitment. Special thanks go to the Ministry of Infrastructure and Water Management, which gave us the opportunity to carry out the exploratory survey, in addition to providing relevant input. Many policymakers, trade associations, top sectors, funding bodies and researchers have been very generous with their time, which made this knowledge agenda possible. I am keenly aware of growing interdisciplinary collaboration, something that is essential to progress in this field. Accordingly, I would like to call on everyone to endorse the importance of further research into microplastics and health.

Jeroen Geurts,
Chair of ZonMw

Juli 2020, Den Haag

Summary

Introduction

Microplastics (the generic term for tiny and very tiny plastic particles) are everywhere. They can enter our bodies through all kinds of routes (such as air, food and water). As yet, the full extent of that exposure and what microplastics are doing in our bodies are still poorly understood. One thing that we do know for sure is that particles of plastic are not broken down to any significant extent. There is also some evidence indicating that they can be harmful in various ways. Levels of microplastics are rising, partly due to the disintegration of litter and to the wear and tear experienced by plastic products, such as garments made of synthetic textiles, car tyres, kitchen utensils, etc. 'Microplastics' is a generic term for particles with a wide range of sizes (ranging from a few tens of nanometres up to half a centimetre), shapes, chemical compositions, etc. Acting on the basis of the precautionary principle, the Dutch and European governments are taking measures to reduce the levels of microplastics in the environment. We need a better understanding of these diverse particles of plastic if we are to take specific, targeted measures and to develop innovations to protect our health.

Assignment

The Dutch Ministry of Infrastructure and Water Management has asked ZonMw to conduct this exploratory survey into the current state of scientific knowledge regarding microplastics and health. It has also asked ZonMw to identify the existing knowledge requirements of the various organisations involved, to deliver a knowledge agenda that will serve as a guide to application-oriented research. Accordingly, this report starts by discussing the current state of affairs (Section 1), followed by an inventory of the knowledge gaps and knowledge requirements in terms of science, policy and innovation (Section 2) and a knowledge agenda that sets out recommendations for a coordinated approach (Section 3). While the knowledge requirements have been identified in The Netherlands, the results may prove useful at international level.

Results

As yet, there is no evidence that microplastics produce serious adverse effects. Yet that statement offers little comfort, as very little is known about the health effects produced by the various microplastic particles. As yet, it is impossible (or virtually impossible) to measure levels of microplastics in the human body. We do not yet have any measurement methods for the very tiniest particles, which can be expected to enter the body quite easily, and even to be absorbed by cells. Risk assessments involve a formula in which hazard is multiplied by exposure. In the case of microplastics, both the hazard involved and the levels of exposure are still very poorly understood. Based on existing knowledge about comparable particles, it is likely that the particulate nature of this material itself is producing adverse effects (particle toxicity). Furthermore, we still do not know how microplastics move through the body, nor do we have any information concerning the extent to which they accumulate in specific cells or organs. In addition to the above-mentioned particle toxicity, these particles may also be capable of carrying chemicals or pathogens into the body. Particles of plastic are encased in a layer of material known as the 'corona' (which has nothing to do with coronaviruses), which may contribute to their chemical and biological properties and the associated risks. As yet, we only have a limited understanding of this.
The inventory revealed that the business community, NGOs, government bodies, top sectors and knowledge institutions need a better understanding of the health effects produced by microplastics, as well as the measurement methods used to identify them. That inventory consisted of a number of interviews, supplemented by an internet consultation. At various stages, the text of this exploratory survey was also discussed by experts and stakeholders from a variety of backgrounds, who appended their comments.

Conclusions and recommendations

It has now been more than 110 years since a patent was granted for Bakelite (the first plastic). However, we still know very little about the impact that the growing levels of microplastics are

having on our health. The first step towards acquiring more knowledge on this subject was based on environmental research and on ZonMw's Microplastics & Health programme (the first of its kind in the world). This step deserves to be pursued in a coordinated way, one that is geared to international developments. One way to foster coherence and focus is to adopt an overarching risk assessment framework. Here, the efforts of people from different disciplines should be combined. There would also be a strong link with the everyday practice of policy and innovation. As soon as new knowledge becomes available, its significance in terms of health impact assessment and potential policy measures and innovations should be examined. Full use will be made of these social and economic opportunities, by means of interdisciplinary cooperation within public-private consortiums.

The input of numerous stakeholders has been used to formulate the main focal areas and knowledge questions (see Table 1 and Section 3). The recommended objectives for the coming five years are:

- **Joint programming based on a health impact assessment framework.** The framework maps out a route from knowledge to solutions, and spotlights any knowledge that merits priority. It also forms the basis for the provisional risk assessment of health impacts and for identifying potentially useful measures. It provides a basis for allocating responsibilities, roles, and tasks to various stakeholders from the policy domain, knowledge institutions, the business community and NGOs. The goal is to establish effective national and international partnerships aimed at mitigating the potential health effects of microplastics.
- **Knowledge of the health effects.** Systematic research involving various model systems (such as tissue cultures, laboratory animals and tissue samples) is the only way to determine, as quickly as possible, which of the theoretically conceivable health effects actually pose a hazard in reality. The very tiniest particles merit special attention, as they are the least well understood but are expected to have the greatest impact.
- **Targeting improved measurement methods and the measurement of exposure:** until such time as the entire spectrum of particle sizes and shapes can be measured, it will not be possible to draw any meaningful conclusions about health impacts and the effects of various innovations and measures. This applies to measurements in both water and air, as well as to measurements in food and in the body (internal exposure).
- **Translating model systems to the human situation:** while fundamental knowledge is indispensable, cell cultures or zebrafish are not human subjects. Nevertheless, there are techniques for extrapolating the results obtained from model systems like these to the human situation. In the end, also epidemiological and clinical data are essential to assess actual hazards.

A great deal of work remains to be done within this multifaceted theme. If we are to generate practically applicable results as soon as possible, it is important to join forces with other initiatives, such as the Dutch Knowledge and Innovation Agendas (which were developed in the context of the current government's mission-driven innovation policy) and other national and international developments focused on water quality, circularity and the environment. In addition, ZonMw advocates the creation of a programme focusing on international cooperation, with a duration of at least ten years. However, that would include various short-term projects designed to meet urgent knowledge requirements. Over the next five to ten years, it will become increasingly clear whether microplastics actually do have an impact on our health and – if so – to what extent. There will also be a better understanding of what the business community, the government and the scientific community can do about it.

Structure of the report

In Section 1 of this report the problem is explained and the objective of the exploratory survey is discussed. The current state of scientific knowledge is briefly discussed. Section 2 focuses on the existing scientific knowledge gaps, and on the knowledge requirements of the policy and innovation domains. Section 3 sets out a knowledge agenda specifying the main priorities for future practice-based research, and putting forward recommendations for tangible actions.

Table 1

Focal areas and knowledge questions

This table summarises the knowledge agenda, indicating its focal areas and the associated knowledge questions. For further details, see subsections 3.1.1 to 3.1.6. As discussed in subsection 3.2 (Sequence and urgency), some of these knowledge questions have not yet been addressed. After all, many of the knowledge questions listed below cannot be resolved until we have first answered some of the other questions.

1 Innovation and policy

- what measures are still needed to mitigate the potential hazards posed by microplastics (or specific categories thereof)?
- what specific measures are already being taken to reduce exposure to microplastics, and how is their efficacy to be measured (e.g. the effect of ventilation on concentrations in indoor air, measures related to microplastics in water, etc.)?
- which measures (or general measures) might have a positive or negative impact on exposure to microplastics? These might include measures related to fine particulates, water quality, soil quality, food safety, or safe production and working conditions.
- what can individual companies and sectors do to help mitigate exposure to microplastics? Also, what impact are existing initiatives having, such as those associated with the circular economy and Safe by Design?
- what economic benefits might be gained if companies were to focus on innovative solutions for the mitigation of microplastics (or specific microplastics)?
- might it be possible to reduce emissions of microplastics by influencing people's/consumers' behaviour (such as their driving style, dealing with waste, considerations when purchasing products) and, if so, how?
- what are the social and economic costs (e.g. burden of disease, productivity, environmental damage) associated with microplastics? In other words, what benefits might a targeted approach be expected to deliver?
- what standards can we set for the concentrations of microplastics (or specific microplastics) in water, air, soil, food and other relevant products?

2 Classification and risk assessment

- which aspects of the health impact assessment have not yet been sufficiently emphasised?
- is a provisional risk assessment an option (and, if so, under what conditions)?
- which health effects are associated with which microplastics?
- which microplastics and which sources of microplastics cause the greatest exposure?
- which microplastics produce the most serious health effects and how do they come into contact with our bodies?
- which plastics are relatively safe in terms of the health impacts of microplastics?

3 Methods for detecting and identifying microplastics:

- derived from various specific plastics;
- of various shapes (spherules, fibres, flakes, etc.);
- with the widest possible spectrum of particle sizes (with a particular focus on very tiny particles);
- as well as varying forms of chemical and microbiological contamination;
- in a variety of substances and organic matrices;
- with a focus on standardising and harmonising measurement methods throughout the entire process of sampling, isolation, extraction and analysis, plus reference materials, including the quality assurance aspect of this process;
- with agreements (including some at international level) on the best way to define outcomes – number of particles, mass, details of shape and composition, etc.

4 Exposure and toxicokinetics

- what is the external exposure (presence in the environment, in outdoor air, in the indoor environment, in drinking water and in food)?
- what is the internal exposure (models for distribution through the various compartments of the body, accumulation in specific organs and tissues)?
- what routes are involved – which pathways do different types of microplastics use to enter the body?
- what mechanisms are involved – how, and at what rate, do microplastics of different types and sizes move across the body's various membranes and barriers (membrane passage rate) and what part does the corona play in this?
- how do the properties change – how do the characteristics of microplastics change (different external and internal environments)?

5 Fundamental research into health effects

- what are the particle toxicities of different types of microplastics?
- what is the particle toxicity of the very tiniest particles of plastic and what toxicological mechanisms of action are involved?
- what are the chemical effects and kinetics of these effects in smaller particles?
- what microbiological hazards are involved (could microplastics transmit viruses, fungi, bacteria or resistance genes, and to what extent does that actually happen)?
- what do studies involving realistic doses of environmentally relevant microplastics or mixtures thereof (more diverse, broken down, contaminated, and especially very tiny particles and fibres) indicate?
- what are the effects of long-term (multi-generational) exposure?
- what part is played by the corona, outside and inside the body?
- what conclusions can be drawn from the comparison with active controls (soot particles, engineered nanomaterials (such as silver particles), silica particles and natural polymers, such as chitin and cellulose)?
- how do we link up with the broader 'exposome' approach, which focuses on the health effects associated with the full spectrum of environmental factors to which people are exposed, and how much of this involves microplastics?

6 Epidemiological studies of health effects

- what occupational diseases, if any, and other indications of health effects are associated with increased exposure?
- can we verify the results obtained from fundamental research in groups of people?
- what are the long-term effects of microplastics in humans, based on cohort studies (past and present)?
- what are the effects of microplastics in specific target groups with either high or low levels of exposure (e.g. living near motorways, socioeconomic health differences)?
- what is the impact of exposure at a young age?
- what part do microplastics play in specific conditions (including chronic conditions)?

1 Background and objective

We are all exposed to microplastics. These tiny particles of plastic are in the air we breathe and in our food and water, and they are in contact with our skin and mucous membranes. There are rising levels of microplastics in the environment, while they are not being broken down to any significant extent. Microplastics taken up by the bodies of laboratory animals cause health impairment. We still know very little about the extent of our current exposure to these particles of plastic, or about their health effects in people. This makes it difficult to protect the population by means of targeted measures and by providing them with reliable information. Accordingly, there is a need to expand our knowledge in various areas.

In 2018, ZonMw initiated the Microplastics & Health programme, to enhance our understanding of microplastics' impact on health. This 15-project programme puts the Netherlands firmly at the forefront of a global effort to uncover the potential health effects of microplastics.
However, this alone will not deliver a solid foundation for policy. The present exploratory survey was commissioned by the Ministry of Infrastructure and Water Management (I&W). It reveals what is already known and highlights key gaps in our knowledge. It also identifies those issues that merit priority, in the domains of science, innovation and policy. The main recommendation is that steps should be taken to encourage further international research, while not losing sight of the need for coordination, coherence, and focus.

1.1 Problem definition

Huge amounts of plastic litter are constantly entering the environment. As it wears away and breaks down, this material becomes a key source of microplastics. Other sources of microplastics include tyre wear, particles of paint and fibres from garments, as well as the wear and tear of plastic food packaging and other plastic objects. Aside from these so-called 'secondary microplastics', there are also 'primary microplastics'. These include the pellets, powders and flakes used as raw materials in the plastics-processing industry, as well as the microplastics that are added to cosmetics and to abrasive cleaning agents, for example (see Figure 1). Thus, environmental levels of microplastics are rising, and this is reflected by an increase in the levels that end up in our bodies.

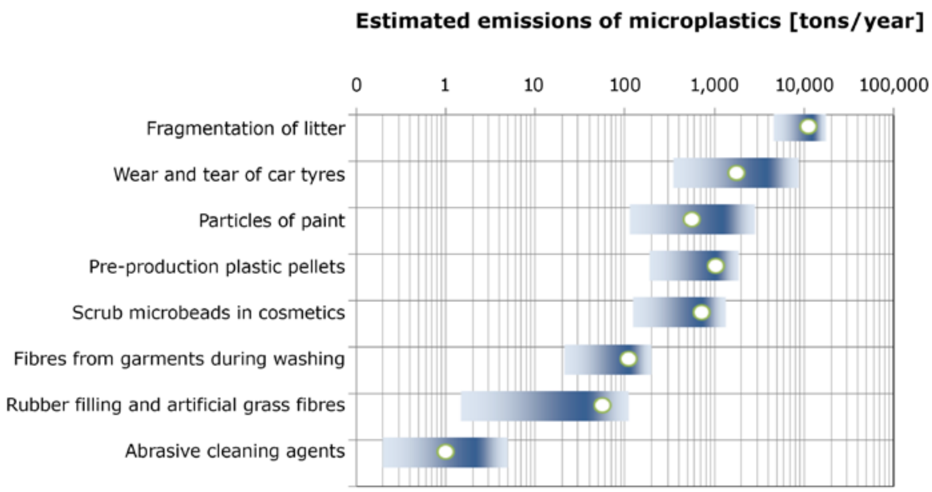


Figure 1 Estimation of the quantities of microplastics originating in the Netherlands that find their way into seawater each year, categorised into the main sources. The columns indicate the margin of uncertainty, while the white dots represent the mean. These are only the emissions to seawater. There are also emissions to groundwater, air and soil, for example. Thus, the total level of microplastics entering the environment is even greater. (Source: National Institute for Public Health and the Environment (RIVM), 2019)

Ongoing ZonMw projects in the area of microplastics and health

The first round of breakthrough projects in ZonMw's Microplastics & Health programme was launched in 2019. It involved 15 projects with individual budgets of €100k–150k, a duration of 12 months and an end date in the fourth quarter of 2020 (delayed by COVID-19). The current round of breakthrough projects represent the very first steps of a research effort to investigate the health effects of microplastics in humans. These projects are fundamental in nature. Their main thrust is to determine whether microplastics can affect health and, if so, to identify the mechanisms involved.

Microplastics are even found inside organs

One study found tiny particles of microplastic in the blood and lymph of mice that had been given food containing this material. In addition, these microplastics were found to trigger inflammatory responses. This effect has not yet been demonstrated in humans. However, previous studies in human subjects have shown that other – comparable – tiny particles (such as fine particulate matter) can enter the blood, brain and amniotic fluid, as well as other tissues and organs. The researchers are currently checking placental tissue, amniotic fluid and blood for the presence of microplastics. Experiments have revealed the following effects in human material outside the body (in vitro). Microplastics are able to pass through the intestinal wall, they are taken up by placental cells, they trigger inflammatory reactions (the basis of many chronic diseases), and they disrupt the function of brain cells and alveoli.

The current studies have delivered key preliminary insights into how and where plastics exert their adverse effects. However, we will need to learn much more before we can perform effective health impact assessments. The leaders of the 15 projects have provided input for the exploratory survey (described in this report), concerning further knowledge requirements.

1.1.1 Physical, chemical and microbiological effects

We cannot specify, with any degree of certainty, the health effects resulting from the rising levels of microplastics in our food, water and air. After all, scientific research in this field has only just begun. What we do know is that, in other mammals, microplastics are taken up by the blood and organs. Furthermore, a number of animal studies have reported adverse effects. We also know that comparable tiny particles, such as those in soot, cause health impairment in humans. So our lack of knowledge about microplastics' harmfulness in humans certainly cannot be interpreted as meaning that microplastics pose no risks for us. Microplastics are likely to impact human health in three different ways – mechanically/physically, chemically and microbiologically.

Particle toxicity

The mechanical/physical effects involved are known as 'particle toxicity', a phenomenon that is believed to be mainly associated with very tiny particles (these are also known as nanoplastics[1]). Particles of plastic are not broken down to any significant extent, nor do they dissolve in water or other substances. Any immune cells that attempt to engulf these particles and break them down will secrete immunomodulating agents (such as cytokines) that can trigger chronic inflammatory reactions. Another way in which very tiny particles of plastic can interfere with cellular function is by generating reactive oxygen species, and by damaging DNA. Given that other nanomaterials have been shown to exhibit particle toxicity, this is quite likely to be the case here as well.

Chemical and biological

The chemicals that are mixed with plastics during manufacture (additives) or that become bound to

1 The terminology used and the associated definitions are not always clear. More specifically, they are not always practical. The 'microplastics' category usually involves an upper size limit of 5 mm. These are still relatively large particles, however, which are not readily absorbed into the body through the bowel. The 'nanoplastics' category usually involves an upper size limit of 100 nm. However, the knowledge gaps addressed by this exploratory survey mainly involve particles with diameters ranging from 100 nm up to 1 µm. Thus, to avoid confusion, we have used the term 'microplastics' here to cover all particles of plastic less than 5 mm in diameter. In the context of health effects, however, the main focus is on particles just a few micrometres in diameter or even smaller (indeed, very much smaller).

microplastics in the environment can have a variety of toxic effects if their concentrations exceed a given threshold value. The kinetics of substances that are bound to microplastics when they enter the body are unlike those observed when the same substances enter through inhalation or ingestion. Finally, plastics and microplastics in the environment can carry bacteria, viruses and moulds, or residual material from these organisms, such as DNA fragments (plasmids) containing genes for antibiotic resistance or virulence.

The 'corona'
With all such effects, the focus should not be on the particle itself, to the exclusion of all else. It is also important to examine the corona – the layer of material encapsulating the particle (which has nothing to do with coronaviruses). This variable layer is very probably involved in the uptake of microplastics into the body, in particle toxicity and in the associated immune response. The corona may also contain chemical contaminants and microbiological components.

Figure 2 Thus, hazards only pose a risk if exposure actually occurs. There are two subtle distinctions that are worth mentioning. Firstly, a threshold value (the minimum level of exposure that results in health effects) is almost always involved. Secondly, as microplastics are not broken down to any significant extent, exposure over extended periods of time is a key factor.

1.1.2 *Health impact*: effect and exposure

In addition to an understanding of the potential hazards, a health impact assessment requires knowledge of the exposure involved (see Figure 2). After all, the hazards mentioned (particle toxicity, chemical toxicity and microbiological effects) will almost always involve a dose/response relationship. In other words, a measurable health effect can be expected once a certain threshold value is exceeded, after which the severity of the effect increases with exposure ('dose').
As yet, however, we only have a limited understanding of the exposure involved. While there have been a number of studies into the presence of microplastics in surface water and drinking water, few have focused on the indoor environment and food, for example. Moreover, even state-of-the-art measuring instruments are unable to detect the very tiniest particles, yet these are the very particles that could penetrate human tissues. With regard to health effects, external exposure is a major factor, but it is not the only one. The subsequent exposure of tissues and organs, plus the possible accumulation of microplastics in the body are also particularly important.

1.1.3 A complex issue

The question concerning the health impacts of microplastics is actually a complex series of questions. 'Plastic' is a generic term for hundreds of different materials that contain a wide range of chemical additives. Microplastics can vary in size (from several tens of nanometres up to five millimetres) and shape (spherules, fibres, flakes). Those that come into contact with our bodies will have followed various routes – via the air we breathe, via our food and drinking water, and via contact with our skin and mucous membranes.
The sources of microplastics and the routes they use to enter our bodies exhibit a similar degree of complexity. In addition, the route taken by a particle before it comes into contact with a human body may affect the chemical and microbiological 'cargo' carried in the corona.

1.1.4 Pragmatic approach

From a policy point of view, this lack of sound knowledge is a serious obstacle. After all, the levels of microplastics in our indoor and outdoor environments are steadily increasing. A pragmatic approach is essential in this regard. Knowledge is needed that will pave the way for a specific course of action, and enable people to make informed decisions. In addition to fundamental knowledge about the health effects associated with different categories of microplastics and an understanding of exposure, it is important to scrutinise existing policy measures. To what extent, for example, do existing measures associated with wastewater treatment, waste management and various regulations already contribute to the mitigation of high-risk (or potentially high-risk) microplastics?

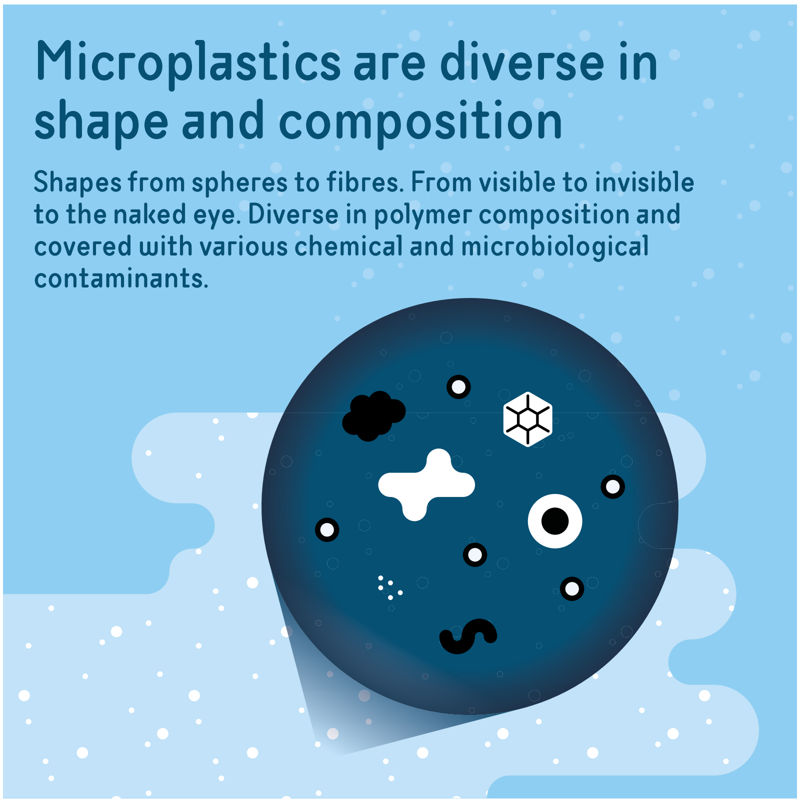


Figure 3 Microplastics are a diverse and variable group. However, models can be developed to arrange them into clear categories for the purposes of health impact assessment.

1.2 Urgency

Research into the risks and health effects of various microplastics is a relatively young field of study, and there are still extensive areas that merit further investigation (see also Section 2). That said, we can already draw a few conclusions about the presence of microplastics in food, drinking water and air. Furthermore, the first exploratory steps have been taken towards developing an understanding of the associated health effects (such as ZonMw's Microplastics & Health programme). This information has been collated into a number of recent reports by the World Health Organization (WHO, 2019), the Science Advice for Policy by European Academies (SAPEA, 2019), the National Institute for Public Health and the Environment (RIVM, 2016, 2017), and others.
Each of those reports emphasises the urgency of the situation. These substances were designed to be persistent, which means that they are accumulating both in our environment and (in all probability) in our bodies. So we need a more solidly based understanding of exposure to microplastics and of the associated health effects. Microplastics of various sizes (up to the current detection limit of about 1 µm) have been found in drinking water, air and a large number of foods. Based on the studies carried out to date, it is likely that the tiniest microplastics can penetrate into the various compartments of our bodies, that they are taken up by cells, and that they contribute to an increased pro-inflammatory tendency. The current state of scientific knowledge is summarised in the text boxes on pages 14-16.

1.3 Scope of the exploratory survey

This exploratory survey highlights the health impacts of microplastics on people. Risks can be calculated from the combination of exposure and effect. Thus, it is all about enhancing our understanding of the health effects of microplastics on the one hand and of exposure (external and internal) to different microplastics over time on the other. This knowledge is an essential prerequisite for the development of policy that can best protect the population. Accordingly, the emphasis is on finding points of reference that can deliver more targeted prevention than current measures (which are based on the precautionary principle). While this exploratory survey focuses purely on the Dutch situation, this is a global problem. Accordingly, the survey's main conclusions are also relevant to the international research effort into microplastics and health.

There is, of course, much more to the issue of plastic and microplastics than the health effects they produce in humans. For instance, it can also be viewed in terms of economics and society, chemistry and production, consumption and behaviour, biology and ecology. Some of these approaches can also be of preventive and precautionary value. For example, the chemical industry can deliver solutions in the area of production processes and the design of new plastics. Furthermore, initiatives in the area of the circular economy can help to reduce levels of plastic litter. The reduction of microplastics could play a more significant part in a variety of decisions, ranging from the choice of road surface to the development of packaging, and from wastewater treatment and agriculture to the design of washing machines. That is important, but it sometimes requires scientific research. ZonMw focuses primarily on research that is directly related to biomedical, epidemiological and prevention-oriented research questions. Accordingly, these will play a pivotal part in this exploratory survey and knowledge agenda.

1.4 Objective and method

The aim of this exploratory survey is to provide guidance for scientific research into the health effects produced by microplastics. This involves drawing up a knowledge agenda that, on the one hand, matches the knowledge requirements in the policy arena and everyday practice and, on the other, is in keeping with the constraints and scope of our current scientific capabilities. Setting priorities is key to this endeavour. Sadly, there is still a gap between what we want to know and what we are actually able to measure.

The goal of this exploratory survey is to bring the microplastics-related domains of science, innovation and policy more into line with one another. Publications in the technical literature and recent reports were consulted to obtain an accurate picture of the current state of scientific knowledge (see Annex 1). A number of scientists contributed to the knowledge synthesis presented in this section, and to the list of knowledge gaps in Section 2. Knowledge requirements in the policy arena and in everyday practice were identified in the course of a series of interviews. Supplementary details were obtained by means of an online consultation. Priorities were jointly established with a delegation from the domains of science, policy and everyday practice (see Annexes 2 and 3 for further details of the method used and the organisations involved).

Health and microplastics: scientific research to date

Environmental scientists have been studying the effects of microplastics on various organisms for some considerable time. In recent years, there has been a greater focus on the associated health effects, as shown by recent reports by WHO, SAPEA and RIVM (see the References section). These pages provide details of the key findings to date. The next section focuses on the knowledge gaps and knowledge requirements.

Exposure and measurement methods

Food

Microplastics have been detected in a range of foods (Van Raamsdonk 2020, and other studies). To date, research into microplastics has mainly taken the form of ecological studies. Accordingly, most of the data collected relates to marine products. Microplastics have been found in fish, shrimp and, in particular, shellfish. We still know relatively little about the accumulation of microplastics in the food chain (Toussaint 2019). Microplastics have been detected in a wide range of products, including sugar, salt, fruit, vegetables, honey and beer. However, in some of these studies the level of quality assurance involved was quite poor.

Water bottles

Plastic water bottles are a well-known source of microplastics. Samples of water from these bottles have been shown to contain many thousands of microplastic particles. Measurements show that many of these particles are smaller than 25 µm, which means that they could potentially be absorbed into the body through the bowel. In the case of many foods, however, we still have no data.
There is evidence that a small proportion of the microplastics that enter the body every day, via the oral route, are absorbed into the body through the bowel. Nevertheless, over the course of a lifetime, a considerable quantity of microplastics can accumulate in the body, depending on the level of excretion (which is unknown) via bile (faeces) and urine. Any microplastics that pass through the gastrointestinal tract without being absorbed could also produce health effects. These could involve direct effects on bowel cells, or the release or resorption of chemical substances, and the transmission of biological pathogens. There is also some evidence that they affect the gut microbiome.

Air

Data on airborne exposure is now starting to become available. We know that fine particulates can potentially cause health problems. A small – but probably increasing – fraction of fine particulates consists of microplastics. The main sources are wear and tear on tyres, and fibres from garments made of synthetic textiles. These fibres, in particular, can be relatively common in the indoor environment. In theory, the respiratory system is quite capable of expelling dust particles (after which they may still end up in the gastrointestinal tract). However, research among textile workers shows that microplastics can penetrate deep into the lungs, and that they have demonstrable effects there, such as triggering inflammatory reactions. There is evidence that microfibres irritate the respiratory system and trigger allergic reactions (RIVM[2]).

Measurement methods

There are various techniques for detecting microplastics, each with their own advantages and limitations. The analysis techniques commonly used to identify plastics include Fourier-transform infrared microscopy (FTIR), Raman spectroscopy and gas chromatography-mass spectrometry (GC-MS) after heating. The latter technique provides no information about the size and shape of the particles. None of the above techniques are suitable for investigating coronas, if these are present. The lower limit of detection is 1-5 µm, depending on the type of equipment being used.

2 www.rivm.nl/microplastics/nieuwe-kennis-over-microplastics-in-lucht

Uptake by the body and biological effects

There are, in theory, two ways to study the health effects of microplastics. One involves investigating exposure and its impact in groups of people (epidemiology), the other entails exposing laboratory animals or tissue cultures to microplastics (toxicology). In toxicological testing in tissue, effective controls can be used for each individual variable. This makes it possible for the particles that are administered to be reliably characterised and defined. To date, commercially available polystyrene beads (which are available in a range of diameters) have often been used for this purpose. Polystyrene nanoparticles can be synthesised in a laboratory. While this approach has produced some interesting initial results, there is some dispute about whether these can be reliably generalised.
Various animal studies have shown that, following short-term exposure to high concentrations of microplastics, particles accumulate in various tissues and organs. Much of this research (which was mostly ecological in nature) involved marine animals. However, accumulation has also been seen in traditional mammal models and in studies in zebrafish.

Physical, chemical and microbiological effects

Increased pro-inflammatory tendency

There is some direct and indirect evidence that particles of plastic have adverse physical effects (particle toxicity). Microplastics are not broken down in the body. Therefore, when they are engulfed by immune cells (phagocytes) this triggers continual activation, and has no effect on the particles themselves. This has various adverse effects, including oxidative stress, the formation of granulomas and giant cells, and the release of various cytokines that trigger inflammatory reactions. Inflammation has been observed in laboratory animals, as well as in people with plastic implants (these release microplastics into the body as a result of wear and tear). An elevated pro-inflammatory tendency (another well-known effect of exposure to fine particulates) is a risk factor for various conditions, such as cardiovascular disease.

Effects in cells

The very tiniest microplastics are able to penetrate cells and trigger various disruptive effects, such as oxidative stress. It has been shown that polystyrene particles can enter the brains of fish, causing demonstrable effects in terms of neurophysiology and behaviour. This has also been found to occur in mice, following exposure via the nose. It is, therefore, quite likely that the same phenomenon might also occur in humans, although there is no conclusive proof of this, as yet.

Chemical substances

We have, however, learned something about the adverse effects of the additives that are often mixed with plastics. Take Bisphenol A, for example. This substance is widely used in the production of plastics and synthetic resins. It causes a wide range of disruptive effects in the body, partly because it interferes with the function of various hormones. Plasticisers (phthalates) have been shown to have similar adverse effects. Microplastics can also release carcinogenic monomers, such as propylene oxide and vinyl chloride. These substances are either left behind during the production process, or are released as the plastics break down. With regard to the substances themselves, less is known about the actual quantities involved, or whether microplastic particles can create high, localised concentrations of these carcinogens, comparable to the levels of medicinal products released by nanoplastics (see 1.2.4.). Furthermore, various substances can bind to microplastics in the environment. These are subsequently released in the bowel or elsewhere in the body. Absorption by microplastics can also have a beneficial effect, as chemicals are excreted more easily via the faeces.

Pathogens in the corona

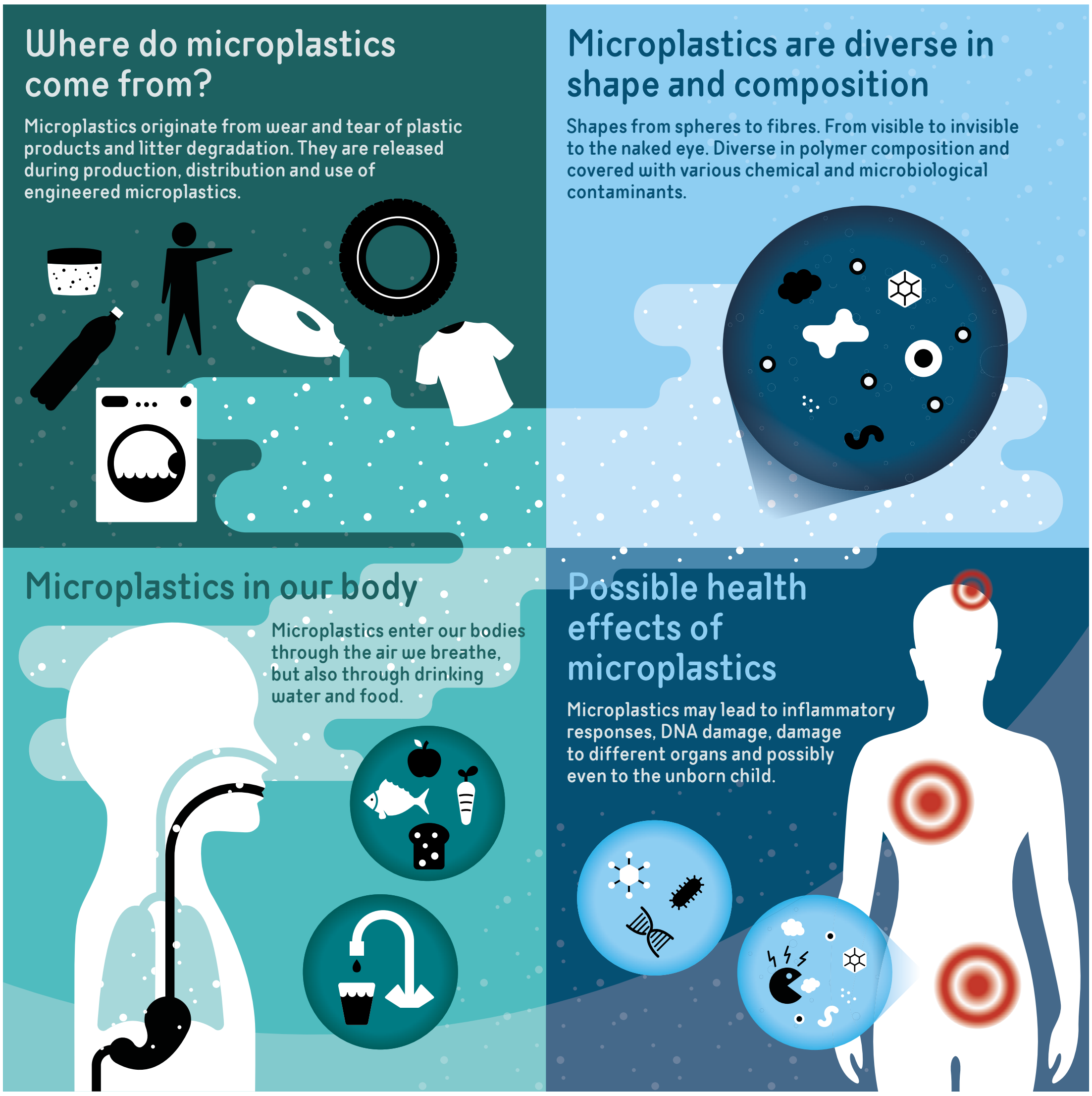
Microplastics are a new and unique element in the environment. The corona that forms around microplastic particles appears to be a rich source of bacteria, including relatively large numbers of opportunistic pathogens. As yet, however, we know very little about the stability of this corona. Moreover, it is not yet known whether antimicrobial resistance is actually transferred between the microorganisms found in these coronas (Skare 2019). Nor is the extent to which viruses, fungi and toxins are disseminated via microplastics well understood.

Medical and cosmetic applications

A logical approach, when investigating the kinetics of chemicals linked to microplastics, is to make use of the growing body of knowledge surrounding the deliberate use of various nanoparticles (engineered nanomaterials, including plastics) in pharmacology. Since the 1970s, very tiny particles (usually smaller than 100 nm) have been used to accurately deliver drugs to a specific target, or for the delayed release of drugs into the gastrointestinal tract. In recent years, degradable plastics have been used for this purpose.
Pharmacokinetic models have been developed to predict the release of diverse substances, in various organ systems, by functionalised nanoparticles designed for this very purpose (Yuan 2019). Pharmaceutical companies have also conducted research into the potential health effects produced by these nanoparticles themselves, in their employees and consumers. These are very specific microplastics, which have been developed for a specific purpose. Nevertheless, such studies and models are a welcome addition to the existing – very limited – body of research into the health effects produced by microplastics, in terms of the chemicals they carry.

Microplastics

Small plastic particles in our body. What are the effects?



2 Knowledge gaps and knowledge requirements

Government and the business community require knowledge to substantiate and evaluate measures and innovations. Based on the precautionary principle, efforts are already being made to limit levels of (micro)plastics in water, air and soil. Despite this, exposure will increase in the coming years, due to the further environmental degradation of plastic materials and to ongoing plastic production. To pursue a more effective policy, it is vital to expand our knowledge of exposure and of the health effects produced by the various microplastics.

This section lists the main knowledge gaps identified in the technical literature and in the course of interviews with key figures from the domains of science, business and government. These will be prioritised in the next section.

2.1 Exposure and measurement methods

As illustrated in Figure 2, an assessment of the actual health impact requires a sound understanding of two principal issues – exposure and health effects (see 2.2). This subsection addresses the measurement of external and internal exposure, the key challenges, the need for standardisation, potential exposure indicators, as well as the importance of using mathematical models and of developing theories.

External exposure

It is difficult to measure exposure. There are several reasons for this. The first problem is detecting microplastics in air, drinking water, food products and other routes through which they can enter our bodies. Obtaining a complete and reliable picture of this situation has proved to be an extremely challenging undertaking. For example, airborne fine particulates include microplastics, but we are not sure of the actual percentage. Also, water filters can only intercept a fraction of the microplastics in surface water, drinking water and waste water. No details are available concerning how many of these (tiny) particles end up in these various compartments. There is a huge gap in our knowledge concerning the presence of this material in food. A great deal of uncertainty still surrounds the issue of whether microplastics are accumulating in the food chain.

Internal exposure

Studying internal exposure and toxicokinetics is an even more complex matter. This is partly due to the sheer diversity of the particles themselves, and to the chemical and microbiological contaminants in their coronas. For example, many questions remain to be answered concerning the presence of microplastics in the human body. How many particles are absorbed daily? How do they become distributed throughout the body? Does accumulation take place and, if so, which organs are mainly concerned? Also, what percentage of particles are ultimately eliminated from the body? Nor is it clear which properties of the particles (shape, electric charge, corona, chemical composition) play a role in these processes, or which tissues and organs contain the most particles.

Challenges

There are, as yet, no adequate methods for some of the areas involved. For instance, tiny particles cannot be observed by light microscopy, nor can they be detected in other ways, particularly when they are embedded in a matrix (or complex matrix). That limit is around 1 µm. This applies to air, water and food, as well as to the human body. In addition, when isolating and extracting microplastic particles from a complex matrix, such as food, tissues or fine particulates in the air, information about the adsorbed chemicals and the corona encasing the particle is often lost.

Standardisation

It is essential for measurement methods to be standardised, to better gauge external and internal exposure (biomonitoring). This applies to the entire process of sampling, isolation, extraction and analysis. It is also necessary to reach agreements on the units in which exposure is expressed. In the case of larger particles, the most appropriate unit would probably be their mass (total mass). For the very tiniest particles, however, their number would be more relevant, in terms of the anticipated biological effects.

Indicators

As our ability to make more precise measurements grows, it will become ever more important to find reliable indicators of relevant microplastic contamination. After all, some types of particles will involve more risk than others. Various feasible, practical solutions for this issue are already available, as in the case of polyaromatic hydrocarbons (PAHs) in drinking water, for example. PAHs are a very large group of substances with varying toxicity. By measuring seven specific PAHs, it is possible to obtain a reliable impression of water quality. Two key characteristics of an indicator like this are that it must be a commonly occurring substance, and that it must involve a relatively high degree of risk. Furthermore, there are many similarities with nanomaterials. Accordingly, expertise in that domain should be leveraged in dealing with the microplastics issue.

Models, theories and classification

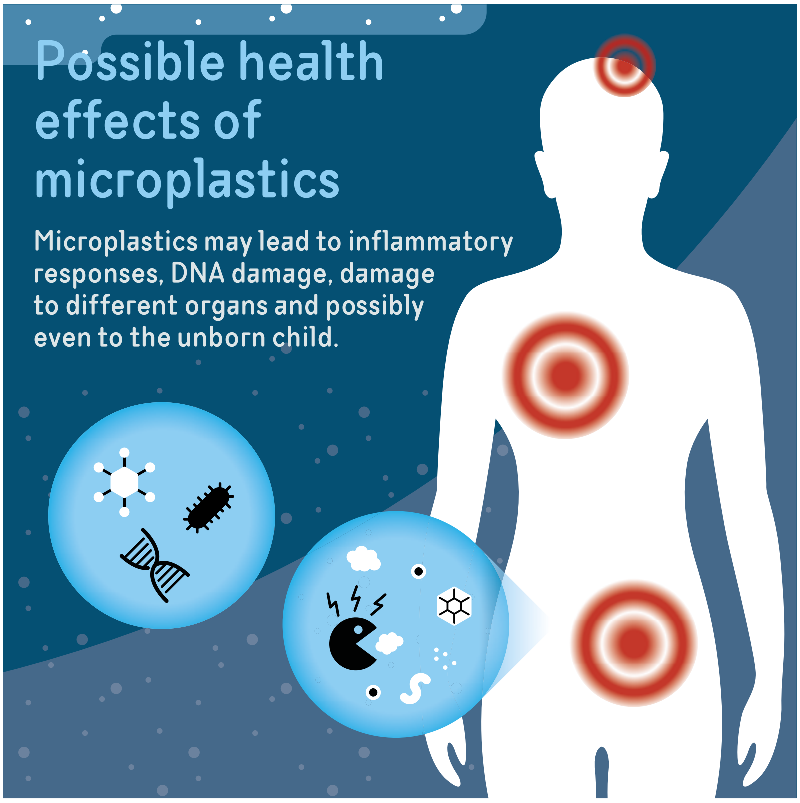
As more knowledge becomes available, sophisticated mathematical models must be developed. These should be designed to handle experimental and epidemiological data on exposure, toxicokinetics, accumulation and the like (see also 2.2). In addition, it will be necessary to develop theories to deal with the enormously diverse range of microplastics. A recently published microplastics classification system is a useful step in that direction. This system, which is based on size, shape and density, renders the above-mentioned complexity of environmental microplastics somewhat more manageable (Kooi and Koelmans 2019). The more data that is generated by objective measurements, the more realistic and relevant these theories and models will become. A greater understanding of the effects and mechanisms of action involved will improve our ability to determine which types and categories of particles are responsible for specific health effects. A worst-case approach can be used to determine which risks merit further investigation and which are of negligible importance (even with the most unfavourable scenarios).

2.2 Health effects in model systems, individuals and groups

Another commonly cited knowledge gap concerns hazards. Systematic toxicological research in model systems (ex vivo and post mortem in tissue samples, in vitro in tissue cultures and organoids, in vivo in laboratory animals) can provide insights into the potential health effects of microplastics, and the underlying mechanisms. As yet, there have been relatively few studies into microplastics that are actually found in the environment, such as flakes and fibres consisting of different plastics, and carrying a range of contaminants. Many of the exploratory studies performed to date used clean polystyrene beads. Environmental kinetics may be a factor, causing the same plastic to have different effects in different environments.

The corona

The part played by the above-mentioned corona has not yet been fully investigated. Coronas have different compositions in the environment than in the gastrointestinal tract, the lungs or other parts of the body. In addition to potential microbiological components, the corona contains proteins, fats and other organic substances which, in turn, may contain metals, toxins and other substances. The corona may well be involved in toxicokinetics (uptake in the body, passage across other membranes, uptake by cells) and in any immune reactions. The corona may also play a key part in the above-mentioned chemical and microbiological effects.



Spotlighting the tiniest particles
The behaviour of the very tiniest particles is probably quite unlike that of larger particles, both in terms of particle toxicity and toxicokinetics. Nor do we know whether specific effects might be passed on to subsequent generations (via epigenetic changes, for example).

Comparison with other materials
This knowledge requirement was mentioned by individuals from the domains of policy, everyday practice and research. To determine whether the observed effects are specific to microplastics, the effects of various microplastics can be compared to those of positive controls, other (sparingly soluble) particles such as soot particles, engineered nanomaterials (including silver particles), silica particles and natural polymers, such as chitin and cellulose. Comparisons of this kind also have practical implications in terms of the policy regarding the microplastics component of fine particulates, for example, or concerning the dialogue with the producers of various materials.

Epidemiological studies
There is a need for epidemiological studies designed to show how the health status of certain groups is related to their exposure (measured or estimated) to microplastics. Even without sophisticated measurement methods, it is possible to compare groups that are most likely to be exposed to increased concentrations of microplastics (workers in the plastics and garment industries, as well as other sectors in which there is elevated exposure, local residents in areas near factories or motorways) with groups that have (or are presumed to have) a low average exposure. In doing so, the challenge will be to distinguish the effect of microplastics from that of other variables (socioeconomic status, lifestyle, fine particulates, etc.).

Target groups
Epidemiological studies could also focus on vulnerable groups, such as children. They may experience a different type of exposure, perhaps because they are more likely to come into contact with house dust, for example, or to put things into their mouths, or to exercise more often on artificial grass pitches, etc. With regard to the potential long-term impact of microplastics, children merit extra attention, from the point of view of prevention. When the effects of microplastics on specific organ systems are better understood, patients with certain chronic conditions should also receive special attention. This includes conditions such as chronic lung and respiratory diseases, chronic inflammatory bowel disease, skin disorders and systemic diseases.

Biomarkers
Mechanistic studies in model systems may yield markers (or biomarkers) that are as specific as possible for the health effects produced by microplastics. This could include specific immune response profiles. These could then be used in epidemiological studies into patients with inflammatory diseases of the bowel or lung, for example. As yet, however, it is not known whether such responses are specific to plastic or whether they are more generic in nature, being triggered by sparingly soluble tiny particles. Fundamental studies may also pinpoint markers that can be used to measure exposure to microplastics or to sparingly soluble particles in general.

2.3 Which microplastics (or sources thereof) cause the greatest health impact?

'Which microplastics (or sources thereof) cause the greatest health impact?' is a particularly relevant question for the business community and the government. This pragmatic research question can be broken down into a couple of sub-questions: 'which microplastics and which sources of microplastics cause the greatest exposure?' and 'which microplastics (or sources thereof) have the most serious adverse effects on people and the environment?'. Given the current state of scientific knowledge, it is not yet possible to answer these sub-questions adequately. Any assessment of the health effects produced by the most common microplastics must be based on the results of toxicological studies, model studies and epidemiological studies (see 2.2), as well as exposure studies (2.1).

To date, studies into the routes by which microplastics come into contact with our bodies have mainly addressed the presence of microplastics in seawater and surface water. It will, of course, continue to be important to focus on this issue, particularly from an ecological point of view. However, there is still a knowledge deficit concerning microplastics that enter our food and drinking water via other routes, such as atmospheric deposition, groundwater and soil. For example, it has recently been shown that microplastics in the groundwater and the soil can penetrate lettuce and other agricultural crops (Li et al. 2020). Some studies have focused on a specific risk posed by microplastics. For instance, a great deal of research has already been conducted into the chemical risks of crumb rubber on artificial grass pitches. However, its particle toxicity is still poorly understood.

2.4 How do the various measures and procedures help?

A targeted approach in policy and innovation must be underpinned by scientific knowledge about the full range of health impairments caused by microplastics. It also requires an understanding of the effects of existing measures and solutions, and of any common ground with other problems.

Policy and regulations

While our scientific knowledge of microplastics and health is still limited, measures are already being put in place, in line with the precautionary principle. Our growing understanding of people's exposure to various microplastics and of any associated effects will eventually enable standards to be drawn up for concentrations in a range of compartments, based on health effects and environmental impacts.

Both in the Netherlands and at European level, an ever growing number of agreements are being reached, and rules formulated, to prevent plastics and microplastics from entering the environment. These include planned regulations in the context of the European REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) Regulation that will prohibit the deliberate addition of microplastics for various applications. At European level, the European Green Deal's aspirations regarding a 'zero pollution action plan for air, water and soil' provide a starting point for new plastics policy. The EU's Marine Strategy Framework Directive provides a basis for preventing pollution of the oceans. Within that framework, the Green Deal on Ships' Waste Chains, the Green Deal on Fisheries, and the Green Deal on Clean Beaches have been concluded in the Netherlands. Health care is also contributing to this effort, by means of the Green Deal on 'The Netherlands on the Way to Sustainable Care'.

Within the Delta Approach to Water Quality and Freshwater Supply (Ministry of Infrastructure and Water Management), efforts are being made to reduce litter (including plastic litter) and to prevent the emission of microplastics from car tyres, textiles, paint and abrasive cleaning agents. Agreements have been reached with various parties within that framework, including an agreement with the business community concerning the use of microplastics in cosmetics. The other avenues being explored include a chain approach to microplastics emitted by textiles and measures implemented by the business community to prevent the loss of plastic pellets (from the plastics chain) to the environment (Operation Clean Sweep). Additional measures are also being tested to reduce the amount of litter in rivers. These include pilot projects featuring floating booms and behavioural interventions (Policy Programme on Microplastics, 2018 [3]). Stientje van Veldhoven, the State Secretary for Infrastructure and Water Management, has concluded the Plastic Pact NL and has also launched the European Plastic Pact. The aim is that, by 2025, industry will only use recyclable and reusable plastic. In addition, her packaging and circular economy policy represents a commitment to making the plastic chain ever more sustainable.

The extent to which these measures might help to reduce the levels of microplastics, and to mitigate their potential effects on public health, has not yet been evaluated. The Ministry of Health, Welfare and Sport is developing policy aimed at achieving a healthy living environment (this covers the Prevention Agreement, Mission-Driven Innovation Policy), as well as food and product safety.

'Linkage' with other areas

Policy in other areas can also have an impact on microplastics. It seems logical that exposure to microplastics might be influenced by the measures and procedures targeting fine particulates, water quality, soil quality, food safete or safe production and working conditions. An exploration of the contributions made by these measures and procedures may help to boost the effectiveness of

3 www.zoek.officielebekendmakingen.nl/kst-30872-219

current and future policies, in terms of reducing exposure to microplastics. The approach (chain approach) used to deal with comparable issues – such as limiting the concentrations of drugs in water – could also be assessed, to determine whether this might be of use in reducing microplastics.

Consumers

Furthermore, the behaviour of members of the public/consumers plays an important part in mitigating exposure to microplastics. For example, driving style, traffic participation and vehicle maintenance influence tyre wear and the creation of fine particulates. Also, non-degradable plastic ends up in kitchen and garden waste and has to be removed. Then there is litter which is a major source of microplastics. Consumer behaviour also has an impact in this regard. For instance, when people purchase more sustainable products rather than disposable plastic products. It is reasonable to ask whether this behaviour could be influenced by government measures, such as the introduction of a deposit on small PET bottles, or indirectly influenced via the media.

Businesses

Individual businesses and sectors could also help to reduce exposure to microplastics. Research can make such efforts even more effective. In addition, the impact of existing initiatives, such as the circular economy and Safe by Design, could also be examined. Safe by Design, for example, could include designing garments that shed fewer microfibres or eliminating the use of harmful substances in clothing production. The development of better and more sophisticated measurement methods is an important step, and the business community could make a useful contribution in this regard. Various research groups within the chemical industry, for example, are already working on the development of such measurement methods.

Inadvertent effects

New challenges have been created by the development of biodegradable plastics, alternatives to plastics and recycling. The hope is that novel materials and approaches of this kind will, in due course, lead to reduced exposure. From time to time, however, any quest for the 'perfect' solution will encounter 'adverse effects'. Accordingly, these new developments must be critically monitored. Plastic packaging may be effectively broken down in a composting installation at a relatively high temperature, but what would happen if consumers were to place such packaging on their own compost heap or discard it into the environment? What microplastics are generated as degradable plastics undergo 'biodegradation'? What are the material properties of recycled plastics, and what impact might these have on anyone who is exposed to microplastics? What steps have been taken to ensure that, during recycling, no toxic additives from the original plastic end up in the recyclate? Especially now, at a time when agreements with the business community are facilitating a more active search for solutions, it remains vitally important to subject any new solutions to scientific scrutiny.

2.5 Environmental impacts and other research questions

As previously stated, this exploratory survey is mainly focused on the health effects produced by microplastics. Naturally, discussions with scientists and policymakers have also touched on relevant research questions that are not directly related to health. Those policymakers in the government, top sectors and business community who are committed to reducing pollution from plastics (and microplastics) also have other important questions. How can we mitigate the creation of microplastics at the source? What requirements should, ideally, be imposed on new plastic materials, on packaging and on other applications? Can those microplastics that are already present in the water or the air be filtered out? And what should we do with this new waste stream? How do microplastics compare to other substances that are relevant to health? Also, what are the health impacts of alternative materials?

One relevant knowledge gap concerns the issue of dealing with plastics in everyday practice. For instance, no data is yet available on the quantity of microplastics released when packaging is opened, or as a result of interactions between food and its packaging. The chemistry of that interaction is well understood, but the release of particles has not yet been properly investigated. For instance, it is unclear whether the acidity of the packaged substance (such as fruit juice) affects the release of microplastics. In many other areas, further research is needed into the creation of microplastics when plastic objects are being used or handled, and the extent to which this contributes to human exposure.

The answers to these kind of questions are relevant to to mitigate the effects of microplastics, as well as human and environmental exposure to them. The long-term impact of plastic waste and microplastics on ecosystems is the subject of ongoing scientific research. We need to explore potential methods for removing plastics (or microplastics) from the environment and/or for breaking them down at an accelerated rate. After all, we still have to deal with a growing mountain of plastic. Given this exploratory survey's focus on the direct relationship between microplastics and health, these questions will play no further part in prioritisation.

3 Focal areas and knowledge agenda

The health effects produced by microplastics merit further scientific scrutiny, as a basis for innovations and policy measures. Consistency and cooperation are key words in this connection. We must make a collective effort to formulate a risk-assessment framework that will enable us to fill in the blanks on the map. Interdisciplinary cooperation within public-private consortiums is the most effective way to ensure that new knowledge is translated into tangible applications as quickly as possible. This will enable us to make full use of these social and economic opportunities.

A consultation round with representatives of the scientific, policymaking and business domains produced a remarkably unified picture of current knowledge requirements in the field of microplastics and health. There is clearly a requirement for more specific knowledge, to underpin more targeted measures. The following were some of the most frequently asked questions on this matter. Which types of plastic and which particles have the greatest impact on health? How do we measure the very tiniest particles, and what are the health effects produced by such very tiny particles? How can we develop standardised measurement methods for the diverse range of microplastics? How do microplastics differ from other tiny particles, such as the soot particles in fine particulates?

3.1 From focal areas to priorities

Based on the general analysis of the problem and on the current state of scientific knowledge described in Section 1, and the knowledge gaps and knowledge requirements set out in Section 2, a number of key focal areas in the field of microplastics and health have been targeted for scientific research over the next ten years. These targets were identified in consultation with experts from the domains of science, policy and business.
The basic principle underpinning this knowledge agenda is that such research (which, in many cases, is still fundamental in nature) should deliver knowledge that meets the needs of those involved in policy and everyday practice, and which can be used to estimate and/or mitigate health impacts. The main consideration is that knowledge must be applicable. To emphasise this fact, we started by listing focal areas on the theme of innovation and policy, followed by classification and risk assessment systems. Based on a discussion of the focal areas, priorities (from ZonMw's perspective) will be set for the upcoming 5-10 years. The following focal areas have been derived from the themes listed in the previous section (these are accompanied by the relevant subsection number, for purposes of clarification).

This concerns the following focal areas:
1. Innovation and policy (2.4)
2. Classification and risk assessment (2.3)
3. Methods for detecting and identifying microplastics (2.1)
4. Exposure and toxicokinetics (2.1)
5. Fundamental research into health effects (2.2)
6. Epidemiological studies of health effects (2.2)

3.1.1 Innovation and policy

This knowledge agenda for microplastics and health is ultimately intended to further the development of targeted innovations in the business community, and of policy measures to mitigate the potential health impacts of microplastics. The aim of this research is to provide clear insights into the risks associated with specific plastics. Hopefully, it will also further our understanding of the ways in which specific microplastics are created. For instance, we will hopefully soon discover whether the microplastics component of the fine particulates that originate from car tyres triggers extra health problems, compared to other such particles. We also hope to find out whether the microplastics in house dust (which originate from paint and garments) produce health effects in children over the course of their lives.

Dialogue

In the upcoming years, scientific research will deliver the knowledge required to subdivide the generic term 'microplastics' into specific categories. Each of these categories can then be furnished with their own health impact assessment (see 3.1.2) and a corresponding specific approach, in terms of innovations and policy. The development of an effective, differentiated approach will require a great deal of effort. After all, experience has shown that academic knowledge does not automatically lead to innovation or implementation. It is often the case that, before this can happen, academic knowledge must first be translated into specific recommendations and measures. This requires effective interdisciplinary interaction between researchers from different disciplines on the one hand, and various professionals (who have to work with the researchers' results) on the other (see also 3.5). Such a dialogue is certainly possible, as shown by the very fruitful conversations that underpin the present exploratory survey.

Knowledge questions in the area of policy:

- what measures are still needed to mitigate the potential hazards posed by microplastics (or specific categories thereof)?
- what specific measures are already being taken to reduce exposure to microplastics, and how is their efficacy to be measured (e.g. the effect of ventilation on concentrations in indoor air, measures related to microplastics in water, etc.)?
- which measures (or general measures) might have a positive or negative impact on exposure to microplastics? These might include measures related to fine particulates, water quality, soil quality, food safety, or safe production and working conditions.
- what can individual companies and sectors do to help mitigate exposure to microplastics? Also, what impact are existing initiatives having, such as those associated with the circular economy and Safe by Design?
- what economic benefits might be gained if companies were to focus on innovative solutions for the mitigation of microplastics (or specific microplastics)?
- might it be possible to reduce the emissions of microplastics by influencing the behaviour of members of the public/consumers (such as their driving style, dealing with waste, considerations when purchasing products) and, if so, how?
- what are the social and economic costs (e.g. burden of disease, productivity, environmental damage) associated with microplastics? In other words, what benefits might a targeted approach be expected to deliver?
- what standards can we set for the concentrations of microplastics (or specific microplastics) in water, air, soil, food and other relevant products?

3.1.2 Classification and risk assessment

As previously stated, 'microplastics' is still very much a generic term. What is needed is an effective classification system for the various types of microplastic, coupled with an assessment of the health impacts (and ecological risks) produced by each category of microplastic. This would be a major step towards preventive policy and the implementation of effective measures by the business community. Preliminary plans for a meaningful classification system are already being prepared. These can be used to guide the prioritisation of exposure studies and studies of health effects.

Framework

In addition to developing a classification system for these particles, it is also useful to consider an overarching risk assessment framework that could help to guide further research. This exploratory survey has already provided key elements to this end. Even though our current level of knowledge is somewhat limited, it is sufficient to carry out a provisional risk assessment, which can then be regularly updated (once every two years, for example). This will generate a series of clear pictures of the current state of affairs, the level of urgency, and any potential solutions. An approach of this kind will also make it possible to identify any new challenges in good time. After all, new materials are constantly being developed, with all the new potential health impacts that this entails. Plastic composites that incorporate carbon nanotubes are a case in point. Due to their unique properties, these materials will be used even more widely in the upcoming years. The question of whether these composites are capable of shedding harmful particles probably merits further investigation.

Health Impact Assessment
The classification of microplastics and the overarching framework can be further refined, in step with our growing understanding of these materials. Ideally, this classification and our understanding of this area would converge. Ultimately, this will result in a solid and practically manageable system that would facilitate a specific Health Impact Assessment for the main types of microplastic, according to the formula: risk = hazard x exposure. In this way, it would be possible to identify those microplastics that merit the most attention, based on the severity of the health effects they produce, or on the degree of exposure and/or accumulation involved. For certain classes of microplastics, it might be possible to designate specific particles as indicators for the entire class, in much the same way as we do for certain chemical substances.

Knowledge questions in the areas of classification and risk assessment include:
- which aspects of the health impact assessment have not yet been sufficiently emphasised?
- is a provisional risk assessment an option (and, if so, under what conditions)?
- which health effects are associated with which microplastics?
- which microplastics and which sources of microplastics cause the greatest exposure?
- which microplastics produce the most serious health effects and how do they come into contact with our bodies?
- which plastics are relatively safe in terms of the health impacts of microplastics?

3.1.3 Methods for detecting and identifying microplastics

The challenge will be to develop methods for detecting and identifying microplastics in a world that is full of tiny dust particles of all kinds. This broad challenge can be subdivided into a number of more specific challenges. The development of measurement methods goes hand in hand with efforts to harmonise and standardise each and every step involved in making a measurement. In the field of measurements, too, every effort should be made to avoid framing microplastics as a generic term.

Methods for detecting and identifying microplastics:
- derived from various specific plastics;
- of various shapes (spherules, fibres, flakes, etc.);
- with the widest possible spectrum of particle sizes (with a particular focus on very tiny particles);
- as well as varying forms of chemical and microbiological contamination;
- in a variety of substances and organic matrices;
- with a focus on standardising and harmonising measurement methods throughout the entire process of sampling, isolation, extraction and analysis, plus reference materials, including the quality assurance aspect of this process;
- with agreements (including some at international level) on the best way to define outcomes – number of particles, mass, details of shape and composition, etc.

Each breakthrough in measurement and detection methods enables us to answer new questions regarding exposure (3.1.4) and its impact (3.1.5 and 3.1.6).

3.1.4 Exposure and toxicokinetics

Before we can determine the health impact of various microplastics, we need data on short-term and long-term exposure. This involves exposure at various levels – in the environment (air, surface water, groundwater, soil), individual external exposure (outdoor air, indoor environment, drinking water, food) and the internal exposure of the body's various organs and compartments. Health effects are, of course, most strongly associated with internal exposure over time. Here, it is important to focus on the elimination of microplastics from the various compartments of the body, and on accumulation, which may involve high levels of internal exposure for specific tissues and organs. In other words, we need to develop toxicokinetic models (or computer models) for microplastics that enter our bodies through a variety of routes. Given the diversity of microplastics, these models will also have to allow for differences in particle size, composition, contamination, etc.

Mechanisms

In various areas, the research required to develop these models goes beyond the measurements described in 3.1.3. After all, we need to find out how – and how rapidly – different particles penetrate the body's various barriers (intestinal wall, blood vessels, placenta, blood-brain barrier, etc.). In addition to quantitative data, this involves an understanding of the mechanisms by which microplastics move through the body. This process will involve similar mechanisms in plants and animals, which has implications for the accumulation of microplastics in the food chain in general and in our own food in particular. In line with the above-mentioned finding that microplastics are taken up by agricultural crops, other studies (whose methodology, incidentally, is still rather controversial) show that very high concentrations of microplastics are present in fruit and vegetables (Conti et al., 2020). Knowledge of this kind is, of course, highly relevant in terms of assessing external exposure, and for developing measures to curtail this. Our growing understanding of the mechanisms by which microplastics move through the body will eventually enable us to develop markers (or biomarkers) that can be used to determine exposure. These methods also make it possible to track exposure over time, and to evaluate the effectiveness of specific measures.

Knowledge questions in the areas of exposure and toxicokinetics:

- what is the external exposure (presence in the environment, in outdoor air, in the indoor environment, in drinking water and in food)?
- what is the internal exposure (models for distribution through the various compartments of the body, accumulation in specific organs and tissues)?
- what routes are involved – which pathways do different types of microplastics use to enter the body?
- what mechanisms are involved – how, and at what rate, do microplastics of different types and sizes move across the body's various membranes and barriers (membrane passage rate) and

what part does the corona play in this?
- how do the properties change – how do the characteristics of microplastics change (different external and internal environments)?
- what is the external exposure (presence in the environment, in outdoor air, in the indoor environment, in drinking water and in food)?
- what is the internal exposure (models for distribution through the various compartments of the body, accumulation in specific organs and tissues)?
- what routes are involved – which pathways do different types of microplastics use to enter the body?
- what mechanisms are involved – how, and at what rate, do microplastics of different types and sizes move across the body's various membranes and barriers (membrane passage rate) and what part does the corona play in this?
- how do the properties change – how do the characteristics of microplastics change (different external and internal environments)?

3.1.5 Fundamental research into health effects

Fundamental research into the health effects produced by microplastics can draw on the wide range of bio-medical research methods used to identify other types of health effect. These include cultured human or animal cells (in vitro), cells directly derived from a living organism (ex vivo), organoids grown from induced pluripotent stem cells, post-mortems and animal studies (in vivo).

Combine and compare
These different model systems can be used to systematically investigate the potential effects of microplastics, such as particle toxicity, the effects of chemicals, and contamination with microbiological contaminants. In the upcoming years, researchers may combine different techniques and use a variety of microplastics to obtain an increasingly clear and specific picture of the biological effects of microplastics. In combination with a better understanding of external and internal exposure, this will enable us to make increasingly realistic assessments of their actual short-term and long-term health impacts. In this connection, there should be a special focus on the particle toxicity of the very tiniest particles, and on elucidating the underlying toxicological mechanisms of action. In the case of particles with a range of diameters, it is also important to systematically compare microplastics with other particles to which people are exposed, ranging from soot and minerals to natural polymers, such as cellulose.
Various key constituent aspects have been listed above. These include the use of environmentally relevant mixtures of microplastics (which may be contaminated), a focus on specific microbiological risks, such as the transmission of viruses or resistance genes, the role of the corona and the potential impact on future generations. One key objective of fundamental research is to develop biomarkers for the health effects of microplastics. Another is to understand the part played by microplastics in certain biological processes, such as a pro-inflammatory tendency.

Knowledge questions in the area of fundamental research into health effects:
- what are the particle toxicities of different types of microplastics?
- what is the particle toxicity of the very tiniest particles of plastic and what toxicological mechanisms of action are involved?
- what are the chemical effects and kinetics of these effects in smaller particles?
- what microbiological hazards are involved (could microplastics transmit viruses, fungi, bacteria or resistance genes, and to what extent does that actually happen?)
- what do studies involving realistic doses of environmentally relevant microplastics or mixtures thereof (more diverse, broken down, contaminated, and especially very tiny particles and fibres) indicate?
- what are the effects of long-term (multi-generational) exposure?
- what part is played by the corona, outside and inside the body?
- what conclusions can be drawn from the comparison with active controls (soot particles, engineered nanomaterials (such as silver particles), silica particles and natural polymers, such as chitin and cellulose)?

- how do we link up with the broader 'exposome' approach, which focuses on the health effects associated with the full spectrum of environmental factors to which people are exposed, and how much of this involves microplastics?

3.1.6 Epidemiological studies of health effects

Epidemiological studies play a key part in translating fundamental research results into model systems for human health. They also serve a watchdog function. However, research of this kind can often be very protracted, especially in the case of prospective studies. After all, it can take many years for most of the anticipated impacts of microplastics on human health to become noticeable. Also, we still have no reliable measurement methods for determining people's external and internal exposure to microplastics.

Start right now

Nevertheless, we can indeed take action right now, to obtain relevant epidemiological data as soon as possible. For starters, it is important to collect health data on those who are exposed to above average concentrations of microplastics in the course of their work. This includes road workers and people working in the garment and plastics industries. Microplastics also merit attention in the context of planned cohort studies, such as the Dutch 'Lifelines' and 'Generation R' cohorts. In future, any study in which tissue samples are collected and longitudinal health data are gathered can contribute to research into the effects of microplastics. Even if the particles in question cannot yet be detected in blood and tissue samples, this will hopefully become possible in the future. If health data are recorded in the meantime, this will facilitate future studies of the relationship between internal exposure and health effects (once it becomes possible to measure internal exposure).

Target groups

When collecting materials and data, it is particularly important to include children and young people as they will be exposed to microplastics for much longer (from the very moment of conception). For example, if fundamental research yields evidence that microplastics have an impact on specific systems (or organ systems), this should immediate be followed by targeted research. That would involve material from patients and healthy individuals, and would help us to better understand the effects in question.

Knowledge questions in the area of epidemiological studies:

- what occupational diseases, if any, and other indications of health effects are associated with increased exposure?
- can we verify the results obtained from fundamental research in groups of people (3.1.5)?
- what are the long-term effects of microplastics in humans, based on cohort studies (past and present)?
- what is the impact of potential exposure from the moment of conception and of exposure during childhood?
- what are the effects of microplastics in specific target groups with either high or low levels of exposure (e.g. living near motorways, socioeconomic health differences)?
- what part do microplastics play in specific conditions (including chronic conditions)?

3.2 Sequence and urgency

The path leading from knowledge requirements to tangible applications is often cyclical in nature, rather than linear. Each answer raises new questions, or only resolves one aspect of the underlying question. In addition, it is important to note that the scientific approach involves a logical sequence of actions and cannot be hurried. On occasion, this seems to be out of step with the sense of urgency and the wish to discover more about the health impacts of microplastics as quickly as possible. For instance, until such time as we have measuring techniques that can detect and identify specific microplastic particles, we cannot measure exposure and must remain ignorant of the associated health impact. This will continue to be the case even after we have developed techniques

to measure these particles but have not yet started to investigate their impact.
However, the message cannot – and should not – be that government policymakers and innovators in the business community will have to spend the next ten years waiting for results. At any given point in time, the most urgent questions must be addressed using currently available methods, to enable more specific measures to be taken as soon as possible. In many cases, it will probably be necessary to repeat this routine again and again, whenever new measurement methods and new knowledge become available.

3.3 Recommendations for scientific research

The above considerations have prompted the following short-term recommendations with regard to scientific research into microplastics and health:

- **Joint programming based on a framework for health impact assessment:** the frame of reference used when prioritising knowledge questions also helps to safeguard coherence in the requisite interdisciplinary research. This serves as a basis for determining the short- and longer-term health impact. This frame of reference is also the basis for all provisional risk assessments and for identifying measures that are at least meaningful ('no regret' measures).
- **Targeting fundamental research into health effects:** systematic research involving the various model systems described above is the only way to find out, as quickly as possible, which of the theoretically conceivable health effects actually involve a hazard in reality (in vitro, in vivo, ex vivo, organoids, post mortem). The very tiniest particles merit special attention, as they are the least well understood but are expected to have the greatest impact.
- **Targeting improved measurement methods and the measurement of exposure:** until such time as the entire spectrum of particle sizes and shapes can be measured, it will not be possible to draw any meaningful conclusions about health impacts and the effects of various innovations and measures. This applies to measurements in water, soil and air, as well as to measurements in food and in the body (internal exposure).
- **Translating model systems to the human situation:** while fundamental knowledge is indispensable, cell cultures or zebrafish are not, of course, human subjects. Nevertheless, there are techniques for extrapolating the results obtained from model systems like these to the human situation. In addition, when all is said and done, without epidemiological and clinical data it would be impossible to assess actual hazards.

Experts estimate that it would take at least five years to complete the fundamental research needed and to obtain adequate measurements of exposure, based on a common conceptual framework. As soon as reasonably possible, work must begin on completing health impact assessments for various types of microplastics, then developing evidence-based measures (in close cooperation with relevant partners in the business community) and evaluating them. This can launch a new cycle, involving a targeted approach, evaluation, new knowledge and innovations/measures.

3.4 Multidisciplinary cooperation, data sharing, infrastructure

This exploratory survey has revealed a growing focus on microplastics and the associated health effects. Some newly emerging consortiums – both at national and international level – are focusing on key research questions in this area. Accordingly, coordination and cooperation are of the utmost importance (more so than mutual competition) if we are to ensure that key knowledge gaps are bridged as quickly as possible, while avoiding any unnecessary duplication of effort. Costly research infrastructure (such as expensive measuring equipment) could, perhaps, be concentrated in a few knowledge institutions, or perhaps just one.

Data access

The data collected should be accessible to others. This is particularly important in the development of toxicokinetic models (see 3.1.4), classification systems and risk assessments (see 3.1.2). One solution is to sign up to new initiatives that are designed to share data and knowledge. Shared research infrastructure also provides opportunities for joint programming and coordination (see also 3.6). The social and economic interests involved are many and varied. Accordingly, it is vital for this issue to be dealt with transparently, including FAIR [4] data and accessible business reports.

Additional disciplines

It is also important to expand the current group of scientists with research interests in the area of microplastics and health. ZonMw's current programme shows the added value to be gained from cooperation between researchers in areas such as environmental science, medicine, toxicology and ecology. Healthcare professionals, health scientists and researchers operating in the area of prevention and working conditions should be actively involved in microplastics research and policy, to a much greater extent than is currently the case. It is also important to link up with the exposome field, in which the pathogenic role of the full spectrum of environmental factors is investigated. This includes the Exposome-NL project (part of the Dutch Research Council's Gravitation programme) and the EU's EXPAND project (part of the Horizon2020 programme). Moreover, it remains important to keep in touch with the world of ecological research, which has been studying microplastics and their biological effects for many years now. The TRAMP project is a particularly fine example of a successful environmental initiative that may also provide useful information concerning the health effects produced by microplastics.[5]

Interaction with everyday practice

In addition to this multidisciplinary cooperation between scientists, with such application-oriented research it is essential to set up an interdisciplinary interaction with those in everyday practice at an early stage. That interaction would entail involving professionals engaged in everyday prevention, innovative members of the business community and policymakers, in formulating research questions and end products. In the case of some research questions, individual members of the public (or citizen collectives) can also make valuable contributions.

International cooperation

International cooperation is yet another key area, given the recent focus and programming by the World Health Organization (WHO), the EU (Green Deal, Horizon Europe, European Food and Safety Authority, European Environment Agency, European Chemicals Agency), the US (Environmental Protection Agency; Health and Environmental Sciences Institute), the New Zealand Ministry for Primary Industries and the business community (e.g. CEFIC-LRI).

3.5 Opportunities offered by practice-based research and public-private partnerships

For various reasons, the Netherlands ranks among the world's leading nations in the area of research into microplastics and health. This offers opportunities with regard to science, in terms of potential economic and societal applications, and for international exchanges. After all, the Netherlands has a long tradition of high-quality research into the ecological aspects of microplastics, particularly in the marine environment. Research into the fundamental health aspects of microplastics has already started, thanks – in part – to ZonMw's Microplastics & Health programme. Environmental factors in general are the third ranking external determinants of disease burden. Thus the contribution made by microplastics in this regard certainly merits further investigation.

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4 FAIR stands for Findable, Accessible, Interoperable, Reusable. See also www.zonmw.nl/en/research-and-results/fair-data-and-data-management/

5 Technologies for the Risk Assessment of MicroPlastics in the aquatic environment; www.stwtramp.nl/

Public-private partnership

The theme of microplastics is ideally suited to public-private partnerships. This is due to the measurement methods and research methods involved, as well as to innovations for mitigating any health impacts. In addition to companies and government institutions, intermediary organisations and NGOs should also be involved. This kind of close coordination between research and application is conducive to the rapid implementation of research results and to the optimisation of social and economic 'gains'. These gains can not only be achieved at the end of the chain – through the mitigation of microplastics in the environment (and indoor environment), food and drinking water – but, probably, at the beginning as well, by materials researchers, producers and consumers. Various sectors could be involved in this effort. These include health care, agriculture and food, climate and water, and the circular economy.

Coordinated approach

Interdisciplinary cooperation based on a widely supported long-term vision is of decisive importance for future success. The emerging consortium formation and cooperation needs to be augmented. This should preferably involve the creation of public-private partnerships involving the domains of science, government and business, as well as members of the public. Microplastics is a broad-based topic that impacts many different sectors (health, food, water, chemistry, fashion, traffic, construction, etc.). Overarching themes like this require problem ownership to be structured in a way that sustains focus on the issue at hand, while making it possible to develop a sufficiently coherent approach. We need to find an effective structure, one that does not entail unnecessary bureaucracy but which can provide the required direction and coherence. To this end, a framework of knowledge development and knowledge application must be developed. A structure of this kind could help to bring about the translation step from science to tangible innovations and policies, while avoiding any duplication of effort within the various national and international initiatives. Indeed, as the research progresses, it will become increasingly important to coordinate knowledge agendas with research programmes, and to promote synergy. ZonMw can help in this regard, by making full use of its roles in identifying knowledge gaps and placing them on the agenda, in funding health research and in encouraging those involved to apply the knowledge developed by this means.

3.6 Conclusion and further steps

The publication of this exploratory survey is the end result of several months' work, with contributions of many. Its publication is intended to mark the beginning of various activities in the domains of policy and research. That will start with the widespread dissemination of this exploratory survey within the Netherlands and elsewhere.

Over the past one hundred years, plastic materials have helped us to solve many problems in health care and other areas. Plastic packaging's contribution to food hygiene, shelf life and, as a result, to sustainability should not be overlooked. At the same time, we are becoming increasingly aware of the adverse effects caused by the billions of tons of plastic that have been produced since the 1950s. Even if the production of plastics were to be terminated today, the levels of microplastics in the environment will continue to increase, as existing plastic materials break down.

Science has given us the ability to design and produce plastics. Now it is time to enlist the help of science once again, to carefully identify the potential health effects of microplastics, to enable the domains of policy and everyday practice to formulate a targeted approach.

Annex

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Annex 2

Method used in the exploratory survey into Microplastics, Environment & Health

ZonMw was commissioned by the Ministry of Infrastructure and Water Management to draw up this knowledge agenda. Knowledge questions from parties in the domains of policy, research and everyday practice were identified and prioritised to arrive at this Microplastics, Environment & Health knowledge agenda. To this end, the following method was used:

Phase 1 Knowledge synthesis

This phase started with drafting a textual representation of our current knowledge and knowledge gaps with regard to the health effects produced by microplastics. This involves the use of existing reviews, supplemented by recent material from various international sources. The leaders of current research projects within ZonMw's Microplastics & Health programme have provided input. In addition, an analysis was carried out in cooperation with RIVM to determine what knowledge is still needed to complete a Health Impact Assessment. Finally, this knowledge synthesis was presented to – and discussed with – an expert panel of researchers and scientists (see Annex 3).

Phase 2 Knowledge requirements

In the second phase, a list of policy and knowledge questions was drawn up by policymakers and those in everyday practice. To this end, 16 interviews were conducted with a diverse group of organisations (see Annex 3). In addition, a public internet consultation was launched. A total of 21 responses were received, containing suggestions for knowledge questions. The knowledge requirements derived from the interviews and the internet consultation were then compiled, resulting in a list of 34 knowledge requirements.

Phase 3 Knowledge prioritisation

The policy questions and knowledge questions gathered from the domains of policy, research and everyday practice were then prioritised. To this end, stakeholders were asked to select what they considered to be the most important 5 to 10 items from the list of 34 knowledge requirements. They were also asked to rank clusters of these priorities. For this purpose, the priorities were classified into four subcategories (exposure and measurement methods; health effects in model systems (individuals and groups); which sources of microplastics pose the greatest health impacts; to what extent are the various measures and procedures effective). A total of 16 individuals completed this prioritisation exercise.

The outcome of this exercise was then discussed with a delegation from the domains of science, everyday practice and policy. The result of this prioritisation exercise confirmed the key knowledge requirements that emerged in Phase 1 and Phase 2.

Annex

3

The individuals and organisations involved

Those involved

Expert panel

Dick Vethaak, Deltares/VU Amsterdam
Susanne Waaijers – van der Loop, RIVM
Ingeborg Kooter, Netherlands Organisation for Applied Scientific Research (TNO)
Bart Koelmans, Wageningen University & Research
Juliette Legler, Utrecht University
Leo Koenderman, UMC Utrecht

Organisations interviewed

Ministry of Infrastructure and Water Management, Sustainable Environment and Circular Economy Directorate
Ministry of Infrastructure and Water Management, Water, Soil and Marine Directorate
Ministry of Health, Welfare and Sport, Public Health Department
Ministry of Health, Welfare and Sport, Department of Nutrition Health Protection and Prevention
Ministry of Health, Welfare and Sport, Department of Sport
TNO
National Institute of Public Health and the Environment (RIVM)
Netherlands Food and Consumer Product Safety Authority (NVWA)
Top Sector Life Sciences & Health
TKI Water Technology
Top Sector Chemistry
Dutch Lung Fund
Modint Trade Association Fashion Interiors Carpets
Plastics Europe
Netherlands Institute for Sustainable Packaging (KIDV)
RecyBEM
National Association of Water Companies in the Netherlands (VEWIN)
KWR Water

Input provided via internet consultation

Association of River Water Companies (RIWA-Rijn section)
Foundation for Applied Water Research (STOWA)
TI-COAST
SHELL
Deltares
Nanoconsult
Milieu Centraal
Plastic Soup Foundation
Koffie en Thee Nederland

Researchers from:
Vrije Universiteit Amsterdam
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