Committee on Safety Measures for Nanomaterials

Report

March, 2009

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* Extracted from research report of the Committee on Safety Measures for Nanomaterials (Toray Research Center, Inc.) commissioned by the Ministry of Health, Labour and Welfare of Japan in FY 2007.

1. Study Background

The “nano” in “nanomaterial” means “one billionth”. One nanometer (nm) is equal to 1/1000 of a micron (micrometer). The term nanomaterial refers to material composed of nanoscale primary particles (molecules). Nanomaterials are known to show unique properties due to the extremely small size of their compositional units. Since nanomaterials have the potential to yield new materials with superior characteristics not offered by conventional materials, proactive research and development are proceeding internationally.

Nanomaterials such as carbon black, silica, titanium oxide and zinc oxide are already in production, and their use is expanding into general consumer products including tires, silicone rubber, cosmetics, and pharmaceuticals. Recent years have also seen research and development on carbon nanotubes, and there are expectations that results of this research will lead to the development of revolutionary products. It is forecast that new nanomaterials will continue to be developed and used in various applications.

No reports have identified adverse effects on the human body from nanomaterials. Although research on the effects of nanomaterials has been conducted worldwide and recently some recent academic papers suggest certain harmful effects on mice under certain conditions, the data necessary to assess the effects of nanomaterials on human health remains insufficient.

The Committee on Safety Measures for Nanomaterials (Chairman: Shoji Fukushima, Director of Japan Bioassay Research Center, Japan Industrial Safety and Health Association) has held seven study sessions with academic experts and specialists and discussed issues to be addressed to plan safety measures for nanomaterials used in consumer products as well as the future direction of such safety measures, based on current development status and nanomaterial applications, the unique properties of nanomaterials, and current scientific findings. This report summarizes those results.

2. Scope of Study

The committee examined safety measures for chemical substances and products containing chemical substances, such as pharmaceuticals and cosmetics, based on overseas trends, the most recent scientific findings, technological advances, etc. The Labour Standards Bureau of the Ministry of Health, Labour and Welfare is responsible for preventing exposure to nanomaterials at workplaces. The Ministry of the Environment is responsible for measures for controlling nanomaterials released into the environment from waste processing operations such as landfill and incineration after disposal, thus these issues were excluded from the topics covered by the committee.

Nanomaterials subjected to examination were nano-order size particles (molecules) of up to about 100 nm, and aggregates of such particles. However at this time, this excluded naturally occurring nanomaterials and unintentionally generated nanomaterials such as impurities and contaminants.

After gathering information on nanomaterials in general, the committee discovered that harmful effects from specific nanomaterials have not been observed nor ruled out. Hence, the committee chose to review safety measures for nanomaterials in general, rather than focusing on individual substances.

3. Current status of development and latest scientific findings

(1) Production volumes and nanomaterial applications in Japan

According to a FY 2007 survey commissioned by the Ministry of Health, Labour and Welfare, applications and production volumes of nanomaterials in Japan are as shown in Fig. 1 and Fig. 2. In this commissioned survey, information on 21 types of nanomaterials already in use or scheduled to be commercialized relatively soon was obtained through interviews with nanomaterial manufacturers and other such sources. Among the nanomaterials surveyed, carbon-base nanomaterials featured the smallest particle (molecule) diameters. The particle diameter of fullerenes is 1 nm or less, while that of single-wall carbon nanotubes (CNTs) is about 1 nm. The surveyed nanomaterials are used in various products such as tires, home appliances, electric/ electronic products, cosmetics, paints, and inks. By type, silica, silver + inorganic microparticles[1], titanium oxide, nanoclays, and zinc oxide are used in a many fields (see Fig. 1). In terms of volumes used, carbon black, silica, titanium oxide, and zinc oxide all led the list (see Fig. 2).

The results of this commissioned survey are described briefly below. Note that information regarding volume used, examples of usage, and benefits of use were obtained in interviews with nanomaterial manufacturers and other sources undertaken as part of the commissioned survey, and partially revised by incorporating data from a research report on safety measures for nanomaterials (Toray Research Center, Inc.) commissioned by the Ministry of Health, Labour and Welfare of Japan in FY 2007.

[1] Usage conditions of typical nanomaterials

(a) Carbon black

The volume of carbon black used in 2006 in Japan totaled approximately 1 million tons. Carbon black is mixed into rubber or resins or added to solvents. Approximately 80% of the carbon black consumed was used in tires, 15% was used in other rubber products, and 5% used to color inks and paints. Carbon black provides benefits such as increased rubber strength, improved electrical conductivity, improved coloring, and enhanced pigment performance.

(b) Silica (crystalline and amorphous)

The volume of silica used in 2006 in Japan totaled approximately 13,500 tons. Silica is used in silicone rubber, FRP, paints, etc. Use of silica provides benefits such as enhanced strength, insulation properties, and water resistance.

(c) Titanium oxide (rutile form and anatase form)

Titanium oxide exists in two crystal forms: rutile and anatase. Anatase converts to rutile at

[1] Silica, alumina, etc. to which silver ions are adhered.

approximately 1000°C. The volume of nanoscale titanium oxide used in 2006 in Japan totaled approximately 1,250 tons. More rutile titanium oxide was produced than anatase titanium oxide. Rutile titanium oxide is used in cosmetic products, paints, and toners, while anatase titanium oxide is used in photocatalytic coating agents, etc. Use of rutile titanium oxide provides benefits such as protection against UV rays, while anatase titanium oxide offers photocatalytic functions that yield deodorizing effects, etc.

(d) Zinc oxide

The volume of zinc oxide used in 2006 in Japan totaled approximately 480 tons. Zinc oxide is used in cosmetic products, etc. Zinc oxide provides benefits such as protection from UV rays and transparency enhancement.

(e) Single-wall carbon nano tube

The volume of single-wall CNTs used in 2006 in Japan totaled approximately 100 kg. Although they are currently mixed into resins or ceramics, research and development is proactively seeking to expand applications. Single-wall CNTs provide the benefits of reduced weight and improved electrical conductivity.

(f) Multi-wall carbon nano tube (CNT)

The volume of multi-wall CNTs used in 2006 in Japan totaled approximately 60 tons. Multi-wall CNTs are used in semiconductor trays, etc. and provide benefits such as added electrical conductivity, enhanced strength, and electromagnetic shielding.

(g) Fullerenes

The volume of fullerenes used in 2006 in Japan totaled approximately 2 tons. Used in sporting goods, fullerenes provide the benefits of increased resilience, reduced weight, and enhanced strength.

(h) Dendrimers[2]

Dendrimers were largely used for paper, with approximately 50 tons of dendrimers consumed in 2006 in Japan for use in paper, and several tons used in cosmetic products. Primarily used in paper as a coating agent, dendrimers provide benefits including control of rheological characteristics in paper applications and water and oil repellency in cosmetics.

[2] Dendrimers are a type of high-polymer material consisting of dendritic polymers or hyperbranched macromolecules with precisely controlled structures. Compared to ordinary high polymers, dendrimers allow easier structure control. Compounds of varied shapes and sizes can be created by combining different components.

(i) Silver + inorganic microparticles

The volume of silver + inorganic microparticles used in 2006 in Japan totaled approximately 50 tons. Silver + inorganic particles are mixed into resins or fabrics, or used in paints, etc. Use of silver + inorganic particles provides antibacterial benefits.

(j) Nanoclays[3]

Approximately 250 tons of nanoclays were used in 2006 in Japan. Nanoclays are used in anti-settling agents for agrichemicals, and in paints etc. Nanoclays provide various benefits, including sedimentation prevention and viscosity adjustment.

[2] Typical products containing nanomaterials

(a) Pharmaceuticals

For pharmaceutical applications, liposomes[4] are used in drug delivery systems (DDS). However, no commercial medicine produced in Japan incorporated nanoscale DDS at the time of the survey, and demand is mainly for research and development purposes. Nanoclays and silica are used in drugs as a drug formulation auxiliary agent. New medicines using fullerenes and dendrimers are currently attracting attention today, and the use of various nanomaterials in pharmaceutical products is anticipated to expand.

(b) Cosmetics

Inorganic nanomaterials are widely used in cosmetic products, including foundation and sunscreens. Of these materials, titanium oxide and zinc oxide currently hold the largest shares. For titanium oxide, an average particle diameter of 20 to 50 nm is commonly used. Nanomaterials for cosmetics application are surface-treated in many cases. At the raw material stage, these nanomaterials are coated with silicone, aluminum hydroxide, stearic acid, silica, alumina, surfactants, etc. The use of nanoscale liposomes in certain cosmetics has also been confirmed.

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[3] The term “nanoclay” refers to a material made by increasing the purity of bentonite, whose main component is a mineral called montmorillonite, and by reducing particle (molecule) diameters to submicron levels. Montmorillonite is believed to be composed of scale shaped crystals having a thickness of 1 nm and a length of 100 nm.

[4] In liposomes, spherical shell structures are formed by lipid bilayer membranes. The size of the structures depends on the manufacturing method and conditions, but diameters range between 20 and 100 nm. Liposomes have a basic structure of biological membranes, and their applications for DDS and biosensors are currently undergoing research and development.

(c) Food

Use of silica, nanoclays, liposomes, and nanocolloidal platinum in food has been confirmed. Silica is used in food, while nanoclays are used as food additives. Use of liposomes containing lactoferrin has been confirmed in so-called health food. Nanocolloidal platinum is used in mineral water, yogurt, etc.

(d) Food containers/packaging

In the field of food containers and packaging, research is currently underway on the use of nanoclays and iron in PET bottles, and their use is anticipated to begin also in Japan.

(e) Textiles

Use of titanium oxide, zinc oxide, silver + inorganic particles, silica, and carbon black for textile applications has been confirmed.

(f) Household products, sundries, sporting goods

The use of silver + inorganic particles in household products and sundries has been confirmed, as has the use of fullerenes and silver + inorganic particles in sporting goods.

(g) Home appliances, electric/electronic products

For home appliances and electric/electronic products, nanomaterials are often used in electronic parts, and the use of fullerenes and multi-wall CNTs in this area has been confirmed. Also, the use of titanium oxide, CNTs, and silver + inorganic particles in filters for home appliance applications has been confirmed.

(h) Paints and Inks

For paint and ink applications, the use of carbon black, nanoclays, CNTs, titanium oxide, etc. has been confirmed in construction paints, automotive paints, ink jet inks, etc.

(i) Other

Carbon black is mixed into the rubber used to make tires.

Silica and dendrimers etc. as a coating agent for printing paper and home-use ink-jet paper has been confirmed as another use.

Fig. 1　Uses of Nanomaterials

	Medicines etc.	Cosmetics	Food, Food containers/ packaging	Textiles	Household products, sporting goods	Home appliances, electric/electronic products	Paints, inks	Other (paper coating, etc.)
Carbon black		○				○△	○	○ Tires
Silica	○	○	○	○		○	○	○
Titanium oxide		○		○	○	○	○△	○
Zinc oxide	○	○		○	○	△	○	
Single-wall CNT						○△		
Multi-wall CNT	△			△		○	○	
Fullerene	△	○			○	△		
Dendrimer	△	○△				△		○
Silver	△					○△		△ Catalyst
Silver + inorganic micro particle		○	○	○	○	○	○	
Iron						○		
Alumina		○				○△	△	
Cerium oxide		△				○		
Polystyrene		○				○	○△	
Nanoclay	○	○	○△			○	○	○ Agrichemicals
Carbon nanofiber					○	○△		△ Blades for wind turbines
Pigment (micro particle)							○	
Fine acrylic polymer micro particle		○				○	○△	
Liposome	○	○	△					
Nano colloidal platinum		○	○			△		○ Catalyst
Quantum dot[5]	△					△		○ Reagents for research applications
Nickel						○		

Note: In the table, ○, △, ○△ mean the following.

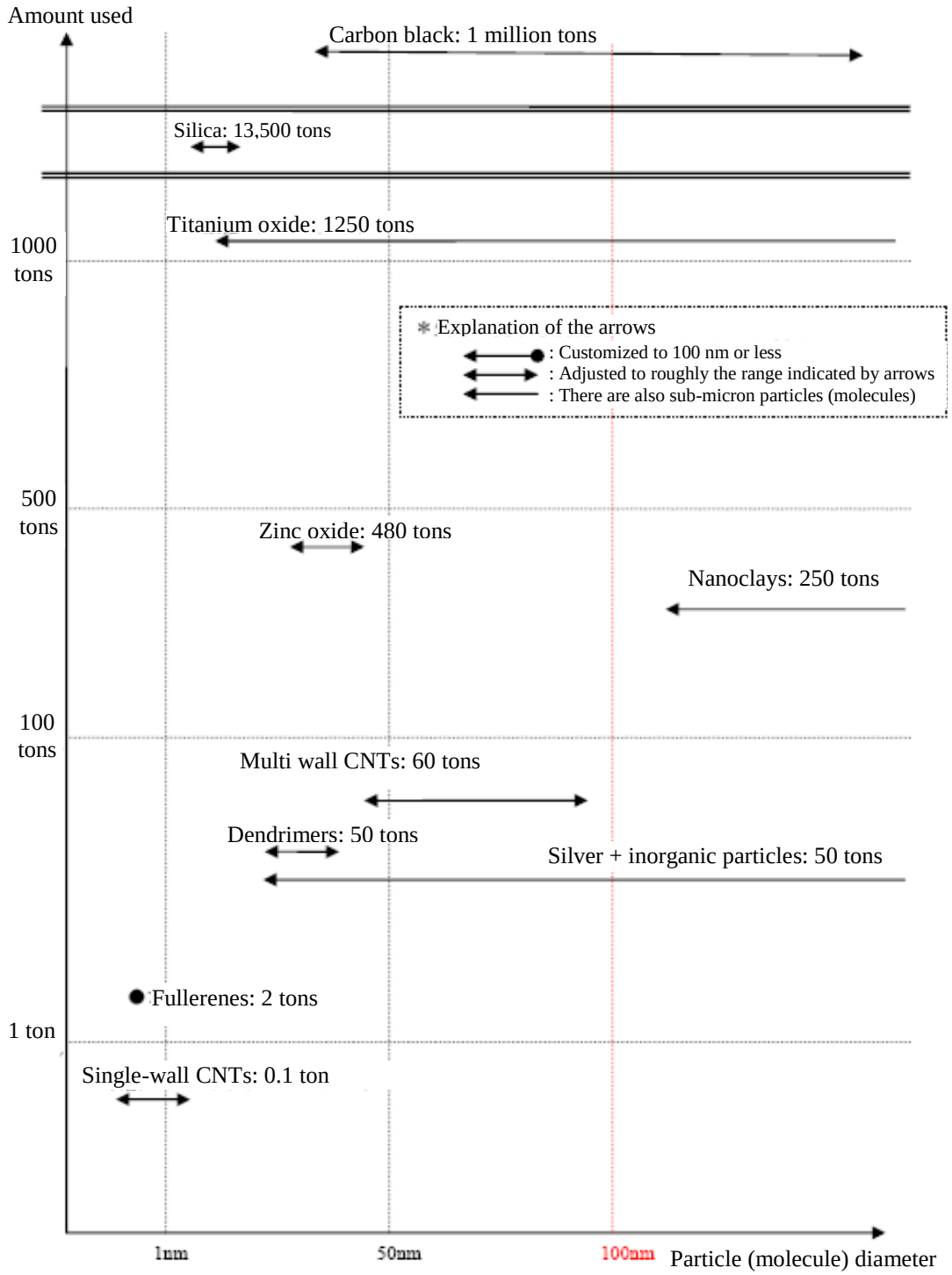
○: Current use;　△: Potential future use;

○△: Field in which applications are expected to expand.

(Excerpt from research report on safety measures for nanomaterials (Toray Research Center, Inc.) commissioned by the Ministry of Health, Labour and Welfare of Japan in FY 2007. Partly revised.)

[5] Quantum dots are artificial molecules obtained by bonding two artificial atoms created by semiconductor fine processing. There are expectations for their use in quantum computers capable of performing ultrahigh-speed computations.

Fig. 2 Volumes of typical nanomaterials used annually in Japan and corresponding particle (molecule) diameters.



(Excerpt from research report on safety measures for nanomaterials (Toray Research Center, Inc.) commissioned by the Ministry of Health, Labour and Welfare of Japan in FY 2007. Partly revised.)

(2) Characteristics of nanomaterials

Many material characteristics, including electrical, optical, and magnetic characteristics, are believed to result from the behavior of electrons in materials. In nanomaterials, extremely small crystal sizes are said to cause changes in the state of electrons within the material, and generate phenomena not peculiar to materials with larger particle sizes. Those indications are that nanomaterials possess characteristics different from those of ordinary chemical substances.

In terms of chemical characteristics, nanoscale particles are said to offer increased reactivity. Chemical reactions basically occur on the surface of a material. Nanoscale materials offer greater specific surface area – surface area per unit mass – and this increased specific area enhances reactivity.

In terms of mechanical characteristics, nanoscale materials are also said to offer greater strength. For example, the strength of single-wall CNTs is estimated to be about 5 to 20 times higher than steel wire, with an elastic modulus approximately 20 times that of steel wire. Reducing the crystal grain size in metals is known to increase hardness.

As for electrical characteristics, applying a voltage to a material generally causes the current to change continuously in direct proportion to the applied voltage. In nanoscale materials, current values change nonlinearly.

With respect to magnetic characteristics, unlike ordinary magnets, which are collections of small magnetic domains, a nanomaterial is itself a single magnetic domain. This is believed to explain their extremely high retaining force.

In terms of optical characteristics, some materials that typically exhibit a metallic luster gain color when converted to nanoscale dimensions. Size can also affect apparent color.

(3) Effects of nanomaterials on the human body

Use of nanomaterials has advanced rapidly in recent years, alongside investigation and research on their potential effects on the human body. No current reports suggest adverse effects on human health. Despite research on the effects of nanomaterials on human health undertaken worldwide, the data needed to assess the effects of nanomaterials on human health remains insufficient.

In searching for information on nanomaterial evaluation methods and nanomaterial safety in the literature extant, we found reports suggesting that certain substances showed cellular toxicity,

inhibiting cell proliferation etc. in *in vitro* experiments. In *in vivo* experiments involving mice and rats, certain substances were reported to cause inflammation reactions etc. in lungs under certain conditions.

Among those materials, multi-wall CNTs have been reported to cause peritoneal mesotheliomas when infused intrapertoneally into mice and administered intrascrotally into rats during the experiment[6]. However, in the experiment, a high dose of multi-wall CNTs was administered intrapertoneally in a way differing from exposure likely to occur in actual situations. Critics have suggested more detailed research is required into the long-term residual properties etc. of the substance based on *in vivo* animal experiments.

Although those reports were found via our review of the literature, the actual sources in question remain nothing more than the fragmentary results of documented experiments. Accepted methods for testing the effects of nanomaterials on living subjects and standards for evaluating toxicity have yet to be established.

[6] Atsuya Takagi; Akihiko Hirose; Tetsuji Nishimura; Nobutaka Fukumori; Akio Ogata; Norio Ohashi; Satoshi Kitajima; Jun Kanno, "Induction of mesothelioma in p53+/− mouse by intraperitoneal application of multi-wall CNT." The Journal of Toxicological Sciences, (2008 Feb) Vol. 33, No. 1 February pp105-116

4. Current Regulations

The Ministry of Health, Labour and Welfare of Japan has jurisdiction over laws concerning safety regulations applying to chemical substances, reviewing the efficacy and safety of each medicine, medical device, and food additive before commercial introduction to ensure safety, etc. For cosmetic products, and containers and packaging used for food products, product standards and criteria as well as a list of substances that can be used as ingredients and those prohibited or restricted for use have also been established as a safety mechanism. For chemical substances found in other general industrial products and household products, various regulations prohibit the manufacture or importing of materials known to pose acute toxicity or chronic toxicity threats. Furthermore, standards and criteria have been established for designated chemical substances based on accumulated scientific data. For commercially available products, a system currently in place mandates the reporting of information on adverse effects of medicines, cosmetic products, and other products; on cases of health damage suspected to be caused by food; and on serious accidents caused by products, including death and injury resulting from the use of consumer products, including household products. At the workplace, regulations based on the Industrial Safety and Health Law protect worker safety and health from hazards posed by chemical substances. Nevertheless, at present, there are no laws that are specially designed for nanomaterials, nor any regulations that focus on the size of chemical substances.

Despite the absence of regulations anywhere in the world particularly targeting nanomaterials, like Japan, the U.S. Food and Drug Administration (FDA), the Commission of European Communities, and other organizations are promoting reviews of safety measures for the nanomaterials found in pharmaceuticals, cosmetics, etc. These agencies have published reports of examination results, which conclude that existing laws are adequate to handle the majority of risks posed by nanomaterials. Hence, no action has begun toward establishing laws or regulations specific to nanomaterials. Given the inadequate volume of data on nanomaterials at this point, critics have pointed to a need to promote information gathering and research, as well as reviews of laws and regulations based on the information collected.[7,8] Thus governments in various countries, including the U.S. and Europe etc., have begun requesting companies to submit information on the safety of

[7] U.S. Food and Drug Administration, "Nanotechnology, A Report of the U.S. Food and Drug Administration Nanotechnology Task Force", July 25, 2007.
http://www.fda.gov/nanotechnology/nano_tf.html

[8] Commission of the European Communities, "Communication from the Commission to the European Parliament, The Council and the European Economic and Social Committee, Regulatory Aspect of Nanomaterials", June 17, 2008.
http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2008:0366:FIN:EN:PDF

nanomaterials.

The Joint FAO/WHO Expert Committee on Food Additives (JECFA), administered jointly by the UN Food and Agriculture Organization (FAO) and the World Health Organization (WHO), undertook a study of nanomaterials used in food additives. According to the JECFA report, JECFA evaluations of food additives have not taken account of possible differences between nanoscale materials and non-nanoscale materials. Instead, it states, in cases where nanoscale food additives have characteristics differing from those of conventional food additives, the results of evaluations of conventional food additives cannot be applied to nanoscale food additives without appropriate revisions.[9]

With respect to nanomaterials contained in general industrial products and other materials, the Toxic Substances Control Act (TSCA), the U.S. law regulating chemical substances, includes no provisions applying specifically to nanomaterials. However, the status of a chemical substance as a new or existing chemical is determined based on whether the molecular characteristics of the substance are the same as an existing chemical substance. Thus, certain nanomaterials, such as CNTs, whose molecular characteristics differ from conventional black lead (allotrope), are defined as new chemical substances. Inorganic nanomaterials differing from allotropes only in particle (molecule) size are not regarded as new chemical substances. The TSCA does not mandate the submission of specified test data for new chemical substances, and applicants are merely required to submit information in their possession to the U.S. Environmental Protection Agency (EPA) before manufacture.

The new EU regulation on chemicals, the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH), may require the updating of registered information on properties when an existing chemical substance is converted to a nanoscale material, but does not specify special handling procedures for nanomaterials.

An overview of chemical-substance-related laws under the jurisdiction of the Japanese Ministry of Health, Labour and Welfare is given below. (A discussion of the Industrial Safety and Health Law is found in the report entitled *Study Group on Preventive Measures for Exposure of Personnel to*

[9] Joint FAO/WHO Expert Committee on Food Additives. Meeting (67th : 2006 : Rome, Italy), "Evaluation of Certain Food Additives and Contaminants: sixty-seventh report of the Joint FAO/WHO
Expert Committee on Food Additives", WHO technical report series no. 940, http://whqlibdoc.who.int/trs/WHO_TRS_940_eng.pdf

Chemical Substances with Unknown Human Toxicity (Concerning Nanomaterials) and is thus omitted here)

(1) Pharmaceutical Affairs Law

The Pharmaceutical Affairs Law of Japan regulates pharmaceuticals, medical devices, quasi-drugs, and cosmetics. In principle, it stipulates the submission of applications for the approval of manufacture and sales for all pharmaceuticals, medical devices, and quasi-drugs before commercialization, and the efficacy, safety and other aspects are confirmed for each product in advance. For all products, including cosmetics, any adverse events generated after product releases must be reported according to established rules to permit the implementation of appropriate safety measures.

[1] Pharmaceuticals

(a) Definition of pharmaceuticals

Pharmaceuticals are defined as (i) items listed in the Japanese Pharmacopoeia; (ii) items, other than machines, instruments, or the like, (excluding quasi-drugs), used for the diagnosis, treatment, or prevention of human or animal diseases; and (iii) items, other than machines, instruments, or the like, (excluding quasi-drugs and cosmetic products), that affect any structure or function of the human or animal body.

(b) Overview of regulations applying to pharmaceuticals

For pharmaceuticals, application for approval of manufacture and sale is in principle required for all products before commercialization. Efficacy, safety, and other characteristics are confirmed for each product in advance. To manufacture or sell pharmaceuticals, the pharmaceutical manufacturer/sales company must obtain an approval of marketing authorization holder, etc.

Following product release, the manufacturer/sales company is required to report information on adverse events and infectious diseases (including countermeasures taken overseas) to the government. Medical personnel and hospital operators, including physicians and pharmacists, are also obligated to report to the government on information of adverse events and similar phenomena, as deemed necessary. Surveys after product release, reexaminations, reevaluations, etc. must proceed according to established systems.

[2] Medical devices

(a) Definition of medical devices

Medical devices are defined as “devices, apparatuses, or similar products used for the diagnosis,

treatment, or prevention of human or animal diseases or those that affect any structure or function of the human or animal body, as designated by government ordinance."

(b) Overview of regulations applying to medical devices

Medical devices are classified into four categories, depending on the gravity of the potential damage associated with equipment malfunctions or failures. Preliminary examination (approval of marketing authorization holder by the government or manufacturing/sales certification issued by a third-party certification organization) occurs before commercialization, except for low-risk items (small steel-made items, X-ray films, etc.). As with pharmaceuticals, medical device manufacturers/sales companies must obtain an approval of marketing authorization holder, etc.

Following product release, as with pharmaceuticals, information on equipment malfunctions and failures is collected and evaluated. Surveys after product release, reexaminations, and other activities must proceed according to established systems.

[3] Quasi drugs

(a) Definition of quasi drugs

Quasi-drugs are defined as products other than machines, instruments, or other such products, having mild effects on the human body, and equivalent items designated by the Minister of Health, Labour and Welfare (medicated cosmetics, hair dyes, vitamin preparations, etc., but excluding medicines), used (i) to prevent nausea, discomfort, foul breath, or noticeable body odor; (ii) to prevent heat rash, sores, etc.; (iii) to prevent loss of hair, promote hair growth, or to remove hair; (iv) to kill or repel rats, flies, mosquitoes, fleas, etc. and thereby to protect humans or animals.

(b) Overview of regulations applying to quasi-drugs

For quasi-drugs, applications for the approval of manufacture and sales are in principle required for each product before commercialization, and safety and other aspects are confirmed for each product in advance. To manufacture or sell quasi-drugs, a quasi-drug manufacturer/sales company must obtain an approval of marketing authorization holder, etc.

Following product release, if it learns about a research report indicating potential harmful effect, the company is required to report the information.

[4] Cosmetic products

(a) Cosmetic products definition

Cosmetics are defined as "products having mild effects on the human body (excluding medicines

and quasi-drugs) and intended for cleansing, beautification, or enhancement of attractiveness and used to modify appearance, maintain the youthful appearance of skin, or to maintain healthy hair by means of application on the body."

(b) Overview of regulations applying to cosmetics

In principle, all ingredients must be indicated on the packaging cosmetic products. When all ingredients are indicated on the product, it is not necessary to obtain an approval of marketing authorization holder. An approval of marketing authorization holder must be obtained in order to manufacture or sell cosmetic products. Following acquisition of the approval, the company must submit advance notification for each cosmetic product to be manufactured/sold.

Cosmetics ingredients are addressed by cosmetics standards, etc. The cosmetics standards specify "prohibitions/restrictions on inclusion of ingredients other than preservatives, ultraviolet absorbents, and tar dyes" (negative list) and "restrictions on the inclusion of preservatives, ultraviolet absorbers, and tar dyes" (positive list) in cosmetics, and permits the mixing of ingredients which do not violate provisions of the standard, provided that the company confirms their safety and selects appropriate substances on its own responsibility.

Following product release, if it learns about a research report indicating potential harmful effect, the company is required to report the information.

(2) Food Sanitation Law

Regulating food additives as well as apparatuses and containers/packaging, the Food Sanitation Law specifies food additives permitted for use based on the completion of prior risk evaluations for each food additive. Specifications and criteria are established for containers and packaging. Containers and packaging that fail to comply with such specifications or criteria may not be sold. If a consumer reports damage to health potentially attributable to food to a public health center, this information is reported to the Ministry of Health, Labour and Welfare by the pertinent local government office. Appropriate measures, such as disclosure of the product name, are then taken.

[1] Food additives

(a) Definition of food additives

Food additives are defined as "substances which are used by being added, mixed, or impregnated into food or by other methods in the process of producing food or for the purpose of processing or preserving food."

(b) Overview of regulations applying to food additives

Manufacture, import, use, sales, etc. related to food additives other than those designated by the Minister of Health, Labour and Welfare are prohibited in principle. Specifications and criteria for the use of food additives have been established as needed. In principle, the additives used in or on food must be clearly indicated on food products, and criteria for the labeling have been established. Products failing to comply with the specifications or criteria may not be sold.

For safety, acceptable daily intake (ADI) levels are set for each food additive, based on scientific data, such as results of substance analysis and animal toxicity tests. Criteria for use are determined based on these ADI and other parameters. Surveys[10] of the daily intake of food additives are carried out by the market basket method. Should any results suggest safety-related issues, necessary measures are taken, such as revisions in the standards applied to food additives.

[2] Apparatuses and containers/packaging

(a) Definition of apparatuses and containers/packaging

Apparatuses are defined as "tableware, kitchen utensils, and other machines, implements, and other articles which are used for collecting producing, processing, cooking, storing, transporting, displaying, delivering, or consuming food or food additives and which come into direct contact with food or food additives." Containers/packaging are defined as "articles which contain or wrap food or food additives and are offered 'as is' when delivering food or food additives."

(b) Overview of regulations applying to apparatuses and containers/packaging

Manufacture or sale of the following items is prohibited:

(i) Apparatuses or containers/packaging which contain or are covered with toxic or harmful substances and involve a risk to human health

(ii) Apparatuses or containers/packaging which touch food or food additives and have a harmful effect on them and involve a risk to human health

(iii) Apparatuses or containers/packaging which do not conform to standards or criteria set by the government

[10] Surveys on the daily intake of food additives are undertaken as part of measures to ensure the safety of food additives. To understand the actual amounts consumed of food additives, types and amounts of food additives in food are examined by the market basket method (purchasing food in supermarkets, measuring the amounts of additives contained in food, and determining amounts consumed of additives by calculations – multiplying the measured amounts using data by the amounts of food consumed in the national health and nutrition examination survey), and the result is examined as to whether it is within the specified acceptable daily intake (ADI).

[3] Other

The Food Sanitation Law etc. stipulate that food-related businesses (manufacturers/sales businesses, etc.) shall have the responsibility to take necessary measures to ensure food safety. Accordingly, companies dealing with food themselves must make efforts to ensure the safety of food.

If a consumer reports damage to health potentially attributable to food to a public health center, the information is reported to the Ministry of Health, Labour and Welfare by the pertinent local government office. If the Ministry of Health, Labour and Welfare receives information from physicians on the health conditions of patients suffering health damage reported by local governments and the information indicates that damage is attributable to intake of food, it makes public the name of the food product, etc.

In addition to product name disclosure, the Ministry of Health, Labour and Welfare can prohibit the sale of said food after hearing the views of pertinent councils, in accordance with regulations specified in the Food Sanitation Law, as necessary to take prompt action to protect the health of citizens from food suspected to cause health damage.

(3) Regulations related to chemical substances etc. found in household products

Main regulations applicable to chemical substances contained in industrial and household products other than pharmaceuticals and food etc. include (i) The Chemical Substances Control Law; (ii) The Poisonous and Deleterious Substances Control Law; and (iii) The Law for the Control of Household Products Containing Harmful Substances. The Chemical Substances Control Law and the Poisonous and Deleterious Substances Control Law regulate the manufacture of chemical substances from the perspectives of chronic toxicity and acute toxicity, respectively. The Law for the Control of Household Products Containing Harmful Substances determines specifications and criteria for designated chemical substances that may occur in household commodities, based on accumulated scientific findings.

[1] The Act on the Evaluation of Chemical Substances and Regulation of Their Manufacture, etc. (The Chemical Substances Control Law)

The Chemical Substances Control Law requires prior submission of notification regarding new chemical substances (i.e., chemical substances not manufactured in or imported into Japan for commercial purposes at the time of the enactment of the Chemical Substances Control Law), and also regulates manufacture, import, and the use of persistent chemical substances that can be toxic to human health or can damage the health of animals and plants if taken continuously, based on their

properties. This law was enacted at a time of rising concerns of environmental contamination by polychlorinated biphenyls (PCBs).

In terms of new chemical substances, safety is basically assessed based on the results of toxicity tests and other information submitted in advance by companies planning to manufacture or import the substances. Safety of existing chemical substances is evaluated based on literature and other information on toxicity collected by the government, in addition to the results of toxicity tests undertaken by the government.

Companies are required to submit notification to the government if they obtain information indicating the chemical products manufactured or imported by them can be chronically toxic to human body. In such cases, manufacture or other activities related to such chemicals are regulated as necessary, based on the information reported.

[2] Poisonous and Deleterious Substances Control Law

The Poisonous and Deleterious Substances Control Law mainly addresses chemical substances, among those commonly circulating in society, as poisonous or deleterious substances posing high risk of causing health damage due to acute toxicity. Currently, 104 items are specified as poisonous substances and 364 items as deleterious substances.

Regarding handling of poisonous or deleterious substances, the Law requires indication of their poisonous or deleterious nature and implementation of measures to prevent theft, leakage, etc. In addition, it regulates transportation, disposal, etc. by determining standards, etc. Businesses manufacturing, importing, or selling poisonous or deleterious substances must be registered and are required to establish facility standards and appoint personnel responsible for the handling of poisonous or deleterious substances.

The government periodically collects information concerning toxicity of chemical substances, reviewing the designation of poisonous and deleterious substances based on the information collected.

[3] Law for Control of Household Products Containing Harmful Substances (Household Products Control Law)

To prevent health damage resulting from the chemical substances used in various household products such as textile products, including outerwear, underwear, and socks, cleaning agents, and aerosol products, the Household Products Control Law specifies various criteria, including the

amount of harmful substances contained, amount of elution, etc., for designated household products. Currently, 20 substances (e.g., formaldehyde) are specified as harmful substances. To confirm and monitor whether commercial products satisfy the applicable criteria, local governments purchase products in the market and test them.

For household products which are not regulated, industries have been advised to establish voluntary standards for each product group to ensure safety. As a result, voluntary safety and sanitation standards are currently established for nine product groups, including wet wipers, insecticides, perfumes/deodorants/deodorizers, contact lens care products, and cotton swabs.

Information on the safety of commercially available household products is collected via local governments, government-designated cities, and special wards. Information is also reported by dermatologists, pediatric hospitals, and the Japan Poison Information Center based on a hospital monitoring and reporting system.[11]

In the event of serious accidents with consequences such as death and injury due to consumer products, including household products, businesses are obligated to report to the Minister of Economy, Trade and Industry in accordance with the Consumer Products Safety Act. Of these reports, those deemed to require response in accordance with the Consumer Products Safety Act, including those indicating potential connections between chemical substances and the accidents, are reported by the Ministry of Economy, Trade and Industry to the Ministry of Health, Labour and Welfare. The Ministry of Health, Labour and Welfare discloses information on these accidents and takes other actions, as necessary.

[11] The hospital monitoring and reporting system is a system for collecting information on health damage (skin hazards, accidental ingestion, inhalation, etc.) caused by household products etc., from dermatologists, pediatric hospitals, and the Japan Poison Information Center.

5. Issues related to and the future direction of safety measures

(1) Issues related to safety measures

The use of some nanomaterials has been expanding into general consumer products. It is predicted that nanomaterials will be used for various purposes through development of various new products using nanomaterials. While no reports indicate adverse effect of nanomaterials on human health, the number of animal testing data is still limited, and the data needed to predict effects on human health is currently insufficient. However, it has been pointed out that the smaller size of particles (molecules) in nanomaterials would result in toxicity differing from that of ordinary chemical substances.

From the standpoint of risk management, it is necessary to promote development of methods to test the effects of nanomaterials on the human body and their physical properties, including simplified techniques, as well as to collect information on the actual use of nanomaterials and their effects on the human body. Also required are *in vivo* and *in vitro* testing, which should be based on those established methods.

Improvement in systems that enable exchange of information on nanomaterials among the government, businesses, and consumers is another issue that should be addressed.

(2) Direction of safety measures

Studies of measures intended to ensure public health should proceed, based on efforts to monitor the status of nanomaterials development and use, to collect information on the effects of nanomaterials on human health, and to proactively provide the information collected to consumers.

Technologies related to nanomaterials are cutting-edge technologies that are still in the nascent stage. Manufacturers of nanomaterials should take the initiative in promoting safety measures from the development phase to fulfill their responsibilities as manufacturers. The government should also work with business to proactively address safety measures for nanomaterials.

(3) Concrete actions to be taken in the future

[1] Collection of information related to the safety, utilization, etc. of nanomaterials.

No current regulations or mechanisms address collection of safety information exclusively for nanomaterials. Still, for medicines and cosmetics, information on adverse events etc. is collected for individual products through the reporting system regardless of whether they are nanomaterials or not. Incidents of health damage suspected to be attributable to food are reported to the Ministry of Health, Labour and Welfare via local governments etc., while information on serious incidents such as

deaths and injuries caused by consumer products, including household products, are reported to the Ministry of Health, Labour and Welfare via local governments etc. and the Ministry of Economy, Trade and Industry.

In FY 2007, a questionnaire survey to manufacturers of nanomaterials commissioned by the Ministry of Health, Labour and Welfare was undertaken for 21 types of nanomaterials currently in practical use or scheduled to enter practical use in the near future, with the goal of obtaining information on domestic production volumes and usage. In addition, review of the literature in order to identify the effects of nanomaterials on the human body and assessment of international trends in safety measures for nanomaterials were also conducted. In FY 2008, detailed information was collected on certain high priority nanomaterials, such as multi-wall CNTs.

Companies are also engaged in tests and research on nanomaterial safety and collecting information through reviews of literature.

The government and companies should pay attention to information on health injuries collected through existing systems, while also proactively acquiring information on the effects of nanomaterials on human health, information on actual use and applications, and information on the volumes of nanomaterials manufactured and imported. In gathering such information, it will be necessary to pay attention to the quality of the information; for example, to confirm whether the information actually pertains to nanomaterials.

It is important to note, for example, that a fact that a substance has no effect on animals does not always mean that it has no effect on human health. Still, potential health effects of nanomaterials should be studied and forecasted in advance to the fullest extent possible by reviewing test and research results, before examining the effects on human health of nanomaterials used in pharmaceuticals, cosmetics, food, etc.

In connection with the above, some pointed out that the priority should be placed on information on cosmetics and food said to contain nanomaterials. Others, on the other hand, pointed to the need to ascertain whether products actually contain nanomaterials, because the use of nanomaterials in such products remains in doubt.

[2] Promotion of testing/research on nanomaterial safety

Through current chemical substance risk research projects funded by the Health and Labour Sciences Research Grants, the Ministry of Health, Labour and Welfare has promoted establishment

of assessment methods regarding the health effects of some typical nanomaterials in order to confirm the safety of nanomaterials, and development of evaluation methods regarding dermal toxicity and methods to visualize disposition of nanomaterials.

The Organization for Economic Cooperation and Development (OECD) has also been promoting tests and research on the safety of nanomaterials. In its first meeting of the OECD's Working Party on Manufactured Nanomaterials in October 2006, member countries agreed to collect information on nanomaterials through international cooperative efforts. An OECD sponsorship program was initiated in November 2007, and the decision was made to produce an assessment report on the health effects of fourteen typical nanomaterials, including fullerenes and single-wall/multi-wall CNTs. In collaboration with relevant ministries and agencies, the Ministry of Health, Labour and Welfare is proactively cooperating with those OECD activities.

The following activities should be continuously implemented and pursued in cooperation with domestic research institutions, based on international efforts by OECD etc. in the area of nanomaterials, with the goal of performing tests based on the methods and testing techniques developed:

- Research on exposure to nanomaterials, including the ways to expose the human body to nanomaterials and evaluation of the exposure, and development of such methods
- Research on the disposition of nanomaterials, such as analysis of disposition in biological samples and measurement of distribution in the human body, and development of such methods
- Research on the toxicity of nanomaterials and species differences in toxicity, and development of test methods
- Development of *in vitro* test methods of nanomaterials, etc.

While numerous exposure paths are open to research, including skin absorption, inhalation, ingestion, and exposure through eyes, research on skin absorption, inhalation, and ingestion is particularly important. The testing and research of nanomaterials should take into account the potential aggregation and dispersion of nanomaterials.

When research results suggest that a nanomaterial has effects on human health, it is essential to analyze whether the effect results from conversion to nanoscale sizes or from the intrinsic characteristic of the chemical substance. If conflicting results are found in previous research, the reasons for the discrepancies should be analyzed.

Some have argued that epidemiological studies should also be conducted with the purpose of

investigating the relationship between the quantity of domestic production of a nanomaterial and certain disease trends, because the establishment of a nanomaterial testing method will take some time. Others have expressed concerns that epidemiological studies would take considerable time.

[3] Collaboration with relevant ministries and agencies
With respect to joint efforts among relevant ministries and agencies, information is currently being exchanged and shared among ministries, with the Cabinet Office positioned as the hub, through science and technology projects such as "Promotion of research and development of nanotechnology and basic research concerning social acceptance," initiated by the Council for Science and Technology Policy. Testing and research on nanomaterials and information sharing should continue to be promoted in cooperation with relevant ministries and agencies and other organizations to establish comprehensive and solid safety measures.

[4] Cooperation with international organizations, etc.
The Ministry of Health, Labour and Welfare is proactively cooperating with the OECD sponsorship program and other activities in collaboration with relevant ministries and agencies. In addition, it is exchanging information with overseas organizations, such as the FDA. These international activities should be continued and strengthened in the future.

[5] Enhanced risk communication with consumers
To proactively promote risk communication, companies should take in opinions on information needed by consumers, collect information on effects of nanomaterials on human health, and disclose or provide the information collected in an easy-to-understand fashion to secure the confidence of consumers. The government and companies should also examine schemes that reflect opinions from consumers more proactively in safety measures for nanomaterials.

With an eye to ensuring consistency with international trends, systematic methods to disclose information and provide product information should be further studied to improve the safety and expand options for consumers. In this effort, the government should disclose information proactively in an easy-to-understand fashion and take steps to ensure transparency – for example, by establishing a website to provide information collected on nanomaterials to the public.

(4) Future issues

Given the current absence of scientific findings that could be a basis for the immediate introduction of laws targeting nanomaterials or regulations focusing on chemical molecular size, it is appropriate to deal with nanomaterials based on existing systems into the near future. Despite the absence of

sufficient information on the effects of nanomaterials on human health or information necessary for forecasting the effects on human health, practical applications of nanomaterials are expected to expand across a wider range of products. Thus, there is a need to carefully collect scientific findings and information pertaining to practical applications of nanomaterials, with the goal of developing test methods for the effects of nanomaterials on the human body, based on considerations of international trends in safety measures. Thereafter, tests based on those test methods developed should proceed.

We should also examine more proactive methods to collect information of nanomaterials, including the current status of advertisements for cosmetics and other products containing nanomaterials and reporting of cases of health damage occurring near manufacturing facilities of nanomaterials, nanomaterial-related accidents and their causes, and long-term effects of nanomaterials on human health. Based on newly collected information, it is appropriate to investigate whether existing systems sufficiently address the safety of nanomaterials, and under the principle of prevention, consider the status of a new system which can be applied to nanomaterials, if needed.

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Past Study Sessions

First session, Monday, March 3, 2008
• Committee scheduling
• Nanomaterials
• Past efforts by the Ministry of Health, Labour and Welfare and others
• Committee program

Second session, Friday, April 4, 2008
• Scope of nanomaterials
• Status of nanomaterials development
• Development of nanomaterial measurement technologies

Third session, Friday, May 2, 2008
• Health effects of nanomaterials

Fourth session, Thursday, November 27, 2008
• Issues involving safety measures for nanomaterials and products containing nanomaterials

Fifth session, Monday, December 22, 2008
• Outline draft of report of Committee on Safety Measures for nanomaterials

Sixth session, Thursday, February 5, 2009
• Draft report of Committee on Safety Measures for nanomaterials

Seventh session, Thursday, March 19, 2009
• Draft report of Committee on Safety Measures for nanomaterials