LRI
The Long-range
Research Initiative

JCIA

Long-term Activities to Support Research into the Effects of Chemical Substances on Human Health and the Environment

Long-range
Research
Initiative
LRI

Japan Chemical Industry Association

What is the LRI?

As part of the Responsible Care* activities of the Japanese chemical industry, the Japan Chemical Industry Association (JCIA) provides long-term support for research into the effects of chemical substances on human health and the environment. These support activities are referred to as the LRI (Long-range Research Initiative). The LRI is funded by JCIA member companies, and receives approximately 200 million yen of funding every year. The LRI is operated in a fair manner based on scientific knowledge.

The LRI is an international project.

The LRI is conducted as part of the voluntary activities of the International Council of Chemical Associations (ICCA). It is a long-term project undertaken in collaboration with the chemical industries of Japan, U.S.A. and Europe (the Japan Chemical Industry Association, the American Chemistry Council and the European Chemical Industry Council).

The LRI has these three major objectives.

- To expand scientific knowledge on health and the environmental impact of chemical substances
- To further improve the capability of safety management of chemical substances and products through the development of new testing and screening methods
- To support public policy decision-making by providing scientific data and understanding

The LRI's six basic principles

- The LRI supports all research into scientific principles and research into the practical application of such principles.
- Research areas subject to support are determined through detailed consideration of research needs with the help of outside experts.
- As a general principle, research themes are selected through public calls.
- The independence of researchers is respected.
- The disclosure and transparency of the research process are ensured.
- Research results are made public.

Propriety, legitimacy, transparency and disclosure of operations

- Outside experts are included in decision-making processes which concern the overall operation of the LRI through the Peer Review Committee*.
- The outside experts are also included in the Planning and Management Panel (PMP), which is in charge of the daily running of research support.
- The outside experts take part in deciding research areas and research topic proposals and in selecting research topics through public calls.
- Research topics are selected by means of public calls and the results of the selections are announced to the public.
- The researchers included in this initiative are required to publish their research results.

Research theses

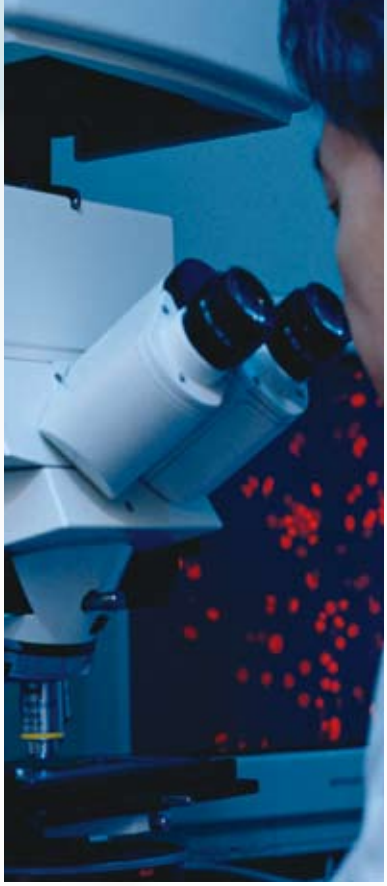
The selected researchers will be requested to compile research results in the form of a thesis and publish this in an academic journal with peer review.
All research that has received support thus far and their research theses are released on our website. Please click on "Research result (thesis)" and "Research report" at http://www.j-lri.org.

Glossary

***Responsible Care:**
Responsible Care is a voluntary activity conducted by each company that handles chemical substances, for the following purposes: To maintain good "environment, safety and health" throughout the processes from development, manufacturing, logistics, usage, consumption and eventually to disposal; to release the results of the activities; and to interact and communicate with society. Responsible Care activities are currently implemented by the chemical industries of 53 countries and regions throughout the world (as of October 2008).

***Peer Review Committee:**
The Peer Review Committee consists of third-party experts for the purposes of ensuring fairness and neutrality and of promoting research having scientifically high standards.

What are the research areas of the LRI?



In 1998, 10 research areas (listed below) were examined by the ICCA and presented in a White Paper as important research areas subject to the LRI. In 2007, the ICCA decided to accelerate the rate of research into the behavior of chemical substances in the environment and inside living organisms.

- Atmospheric chemistry
- Ecosystem dynamics
- Environmental and human exposure assessment
- Neurotoxicity
- Risk assessment methodology
- Chemical carcinogenesis
- Endocrine disruption, including reproductive and developmental effects
- Immunotoxicity and allergies
- Respiratory toxicity
- Epidemiology

The JCIA joined the LRI in 2000, and has been supporting research in the 3 areas of endocrine disruption, chemical carcinogenesis and immunotoxicity (hypersensitivity) with consideration for the 10 areas listed above and the unique characteristics of Japan. The JCIA later added 2 more areas, and is currently conducting support activities in the following 5 research areas:

Research areas supported and promoted by the JCIA/LRI

Endocrine disruption

- What is the true nature of the mechanism of endocrine disruption, which has been shown to affect the reproductive organs and fertility of humans and wildlife?
- If there are adverse effects, are there any test methods that can precisely detect them?
- In order to examine the effects on wildlife, is it not necessary to first understand their habits and "normal state?"

Neurotoxicity

- What are effective methods for investigating the effects of chemical substances on the nervous system, particularly during developmental stages such as the fetal and infant stages?
- What mechanisms affect the nervous system?

Immunotoxicity

- Is there any correlation between chemical substances and eczema/asthma, the number of sufferers of which is thought to be increasing?
- What is the best method for easily discovering chemical substances that cause allergies?
- Are so-called "chemical substance hypersensitivity" symptoms actually the effects of chemical substances?

Chemical carcinogenesis

- What is the best method for easily and rapidly investigating the presence of carcinogenicity?
- What are the carcinogenic mechanisms of chemical substances?
- Even if a chemical substance is carcinogenic, is it not true that this may not affect the organism depending on the amount of intake?

Improving the precision of risk assessments

- Can the precision of assessments carried out when examining the adverse effects of a chemical substance be improved by understanding the behavior of the chemical substance within living organisms and the environment?

Research into endocrine disruption

Endocrine disruption has been commonly known as "environmental endocrine disruption" in Japan since the late 1990s. The JCIA started tackling the endocrine disruption issue even before joining the LRI in 2000. Currently, we are continuing to support research, mainly in the area of understanding actual wildlife conditions.

What are actual wildlife conditions in Japan?

Research into wildlife

We often hear the statements, "Isn't some kind of abnormality occurring to wildlife? Is this abnormality being caused by effects of chemical substances?" In particular, the possibility that the chemical substances called "environmental endocrine disrupters" are affecting organisms in the environment is often discussed, heightening public interest in this area.

However, various wildlife species generally live by evolving under the given conditions of, and adapting to, the environment which they inhabit. Therefore, in order to analyze the effects of changes to the environment outside their habitats, it is important to clarify the "normal state" of the organism in question and obtain basic knowledge on such subjects. Once such a basis of knowledge has been established, we can then develop test methods to properly evaluate the effects and appropriately interpret research results.

The LRI continuously supports field trials conducted in order to understand actual wildlife conditions, including basic research into wildlife and changes to individuals (population) and groups. Thanks to such constant activities, the actual conditions of various species of wildlife are gradually being unveiled.

Killifish

Dace

Upogebia

Earthworm

Are there any endocrine disruption test methods that have been internationally determined?

Research into testing guidelines

Consistent international test methods for evaluating endocrine disruption are needed throughout the world. Under circumstances in which numerous test methods are proposed, guidelines for such test methods are being devised under the leadership of the OECD (Organization for Economic Cooperation and Development). The LRI provides cooperation for validation tests, and supports research into mechanism clarification, which helps the development of test methods.

Research into neurotoxicity

Until recently, well known effects of some chemical substances on the nervous system were those on workers. In recent years however, interest in the possible effects on children's brains and nervous systems, such as hyperkinesias, learning disorders and autism, has increased.
The LRI targets neurotoxicity, particularly the effects on the nervous system during the developmental stage.

Are there any methods for investigating the effects of chemical substances on the development of the brain and nervous system?

Test methods and basic research into developmental neurotoxicity

Guidelines for the evaluation of, and test methods for, the effects of chemical substances on the brain and nervous system using animals have been determined. However, it is true that there are still areas to be improved and developed in such guidelines.
The LRI supports research that facilitates the development of new test methods and the improvement of existing methods.

Major research areas include : Tests regarding learning and memory
Emotions and spontaneous activity
Detailed histopathological examinations

Furthermore, in order to evaluate numerous chemical substances in detail, accurate, precise, highly sensitive, rapid and economical screening tests* are required.
The LRI supports basic research that can help to establish precise screening test methods as well as other test methods.

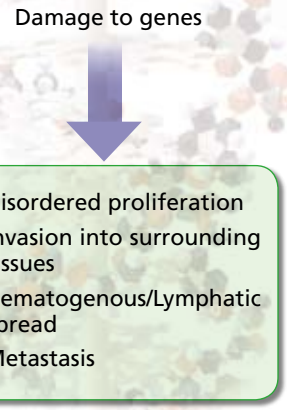
Major research areas include : Changes to genes during the developmental stage of the nervous system
Screening methods using cultured cells

Glossary

*** Screening:**
The term screening means separation or screening inspection. While "filtering" means to separate necessary item(s) from unnecessary item(s), the term "screening" is used when selecting item(s) that meet certain conditions.

Research into chemical carcinogenesis

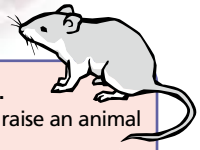
We have been providing support for research into chemical carcinogenesis as an essential area of research since 2000, when the JCIA began participating in the LRI.



What causes cancer?

Research into carcinogenic mechanisms

The LRI investigates various aspects of the carcinogenicity of chemical substances.
It is thought that cancer can develop when genes in normal cells become damaged, thus damaging the cells' normal characteristics and causing abnormal behavior of the cells, as shown in the left-hand figure. At the same time, it is known that cancer can also develop when our original defense functions, such as gene restoration, cell death (apoptosis) induction and cell cycle monitoring, fail.
Research into such mechanisms will eventually lead us to the development of methodologies to easily and precisely detect the carcinogenicity of chemical substances.



In animal experiments….
- It takes 1.5 – 2 years to raise an animal subject.
- It takes another year to determine whether cancer is present or not.
- The cost of an experiment is approximately 200 million yen.

For example….
- Use of cells in which a large amount of carcinogenic genes have developed
- Use of cells that have carcinogenic characteristics due to contact with genotoxic/non-genotoxic carcinogenic substances
- Tests using animals that do not have cancer repressor genes
- Modification of animal characteristics through medicinal treatment

Is it possible to detect chemical substances that may cause cancer?

Research into detection methods

Because a conventional animal experiment takes a long time and requires great expense, the LRI is focusing on the development of methods for easily detecting carcinogenicity at the cell or test tube level, particularly methods for detecting chemical substances that may cause cancer even though they do not directly damage genes (non-genotoxic carcinogenic substances).
This effort will also contribute to the protection of animals.

How much of a carcinogenic substance is needed for cancer to develop in an organism's body?

Research into the threshold value

Since a single molecule of a chemical substance that may directly affect genes (genotoxic carcinogenic substance) can damage one area of a gene, the following hypothesis had been believed until recently: There is no specific lower limit to the amount of the substance needed to cause cancer (i.e., the threshold value*) for genotoxic carcinogenic substances.
In recent years, however, it is believed that there are numerous mechanisms which repair damage to genes. In addition, the presence of a threshold value has come to be proved on an experimental basis.

Glossary

* Threshold value:
It is thought that a reaction does not manifest in a chemical substance until it exceeds a certain dosage, and that it does not affect humans and other living organisms until they are exposed to a certain dose of the substance. The minimum amount of the substance required to cause the effect (reaction) is referred to as the threshold value.

Research into immunotoxicity

It is said that the number of people who have allergies such as eczema and asthma (hypersensitivity) are increasing in industrialized countries. Because chemical substances are said to be one of the potential causes of these conditions, along with changes in diet and living conditions, the LRI supports research from an immunological perspective.

Can new test methods be developed?

Research into development of test methods for sensitizing potential of chemical substances

The LRI supports research conducted in order to analyze the developmental processes of allergies at the tissue, cell and gene levels. Such research will lead us to the development of new testing methods that have even higher accuracy, as well as alternatives to animal testing.

Are there any new evaluation techniques?

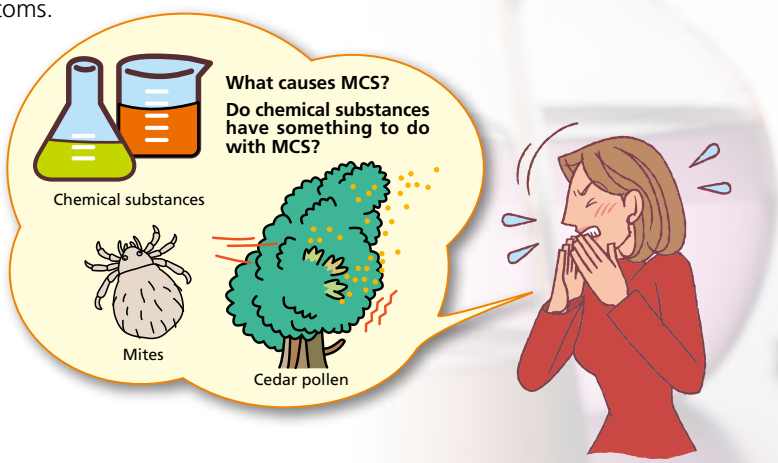
Research into immune reactions and allergy development mechanisms

The effects of chemical substances on immune reactions and allergy development mechanisms are extremely complex. For this reason, new facts are being discovered all the time in the field of immunology.
Based on these newly discovered facts, the LRI supports research into the establishment of new evaluation techniques.

Do chemical substances have something to do with immunity?

MCS (Multiple chemical sensitivities) and immune reactions

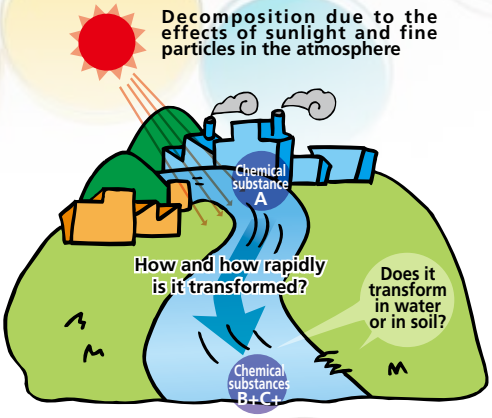
Recently, the presence of multiple chemical sensitivities (MCS) has been reported. MCS can be caused by changes in diet and living conditions, as well as excessive stress. The LRI promotes research conducted in order to scientifically clarify the causes of MCS in order to eliminate these causes and alleviate the symptoms.



Long-range Research Initiative

Research into improvements in the precision of risk assessments

This research area has been designated as a common theme between the LRI in Japan, U.S.A. and Europe for the purpose of improving the precision of risk assessments for chemical substances. In the JCIA, we began providing support in this area in 2007.



How is a chemical substance transformed in the environment?

Establishing a chemical substance transformation prediction system

For example, when chemical substance A is discharged into the atmosphere, it is decomposed by sunlight and fine particles, thus allowing it to be converted into substances B, C etc. by the time it reaches the human body. The speed and form of such transformations can be affected by a variety of environmental conditions. Therefore, it is possible to predict that it can be further transformed within soil and water systems.
Therefore, when conducting an assessment of the health effects of chemical substance A, it is more important to test substances B, C etc., rather than testing the substance A itself.

Can the gap between humans and animals be eliminated?

Research conducted for the purpose of improving the accuracy of methods for predicting hazardous properties

In order to predict the hazardous properties of chemical substances, animal experiments are conducted. However, the metabolic system and metabolic rates of humans differ from those of animals, even for the same chemical substance. If such differences can be eliminated using prediction methods, the precision of assessments of health effects will be greatly improved.

Publication of the LRI research results

[Publications and Presentations]
Once a year, we select some outstanding research and hold a publication and presentation meeting, which is attended by many. The Publication and Presentation meeting is open to public.

[Annual Report]
The Annual Report is issued for the release of each year's research results. The Report can be also viewed on our website (http://www.j-lri.org/).

LRI Office, Japan Chemical Industry Association
Sumitomo Rokko building, 1-4-1 Shinkawa, Chuo-ku, Tokyo, Japan 104-0033
Tel : 03-3297-2575 Fax : 03-3297-2612
URL for JCIA : http://www.nikkakyo.org/
URL for LRI : http://www.j-lri.org/
E-mail address for LRI : lri@jcia-net.or.jp

Responsible Care®
OUR COMMITMENT TO SUSTAINABILITY