

Editorial

Immunotoxicity Risk Assessment for Chemicals and Regulatory Science

A regulative regime for the safety of chemicals in zone of life has been rapidly established on the basis of the advance of toxicology and related science. Especially, the application of risk analysis based on the toxicology has facilitated scientific decisions and administrative actions for the security of chemical safety.

However, their decisions and actions on safety issues have not always gained social consensus. One of the reasons was the impertinent in the practical use of scientific knowledge to cope with issues of health and environment which are in need of administrative actions, that is to say, the inappropriateness of decision making by “the regulatory science”.

Regulatory Science

Regulatory science is an effective science to justify the decision making processes for administrative actions. Particularly, in the safety assessments of chemicals, it is requisite as a theoretical concept to complement the uncertainty of scientific knowledge so that the decision of administrative actions can be adequate in both science and society.

So as to reduce the uncertainty of scientific knowledge, it is important to improve the quality of the bridge introducing products of science to society, although regulatory science is available as the bridge.

From the viewpoint of the contribution of regulatory science to regulatory decisions, regulatory science possesses mainly three functions. The first is to provide tools to produce data. The second is to assess submitted data. This process involves many stages of evaluation, from direct assessment of data to more indirect appraisal of response or impact in society. The third is discussing how to consider and how to balance various factors for regulatory decisions. All three functions are indispensable to the optimal introduction into society of a new product of science, such as discovered substances, tools and technologies as well as knowledge and information.

Therefore, the regulatory science is just an indispensable domain to effectively apply risk analysis.

Risk Analysis

Risk analysis based on toxicology is defined as a process consisting of three components, namely risk assessment, risk management and risk communication (WHO/FAO, 1995).

Of risk analysis, risk assessment is a scientific procedure to assess the risk level or to infer the risk profile, that is to say, it is the scientific evaluation of known or potential adverse health effects resulting from human exposure to chemical hazards. This assessment includes not only quantitative risk assessment but also qualitative expressions of risk and an indication of the attendant uncertainties.

Risk management is the process of weighing policy alternatives, decision-making and action taking, that is to say, the process of devising means to accept, minimize or reduce assessed risks and to select and execute appropriate options. Risk communication is an interactive process of exchanging information and views on risk among risk appraiser, risk managers, and other concerned parties.

Risk Assessment

Risk assessment of adverse health effects in human from exposure to a particular agent is performed on the basis of scientific data mostly derived from toxicological studies on the agent. Its process is composed of four main steps; hazard identification, hazard characterization (or dose-response assessment), exposure assessment and risk characterization. However, there are several issues of uncertainty in the scientific knowledge of chemical risk assessment assessed on the basis of animal-tests as follows (WHO/FAO, 1995) (IPCS, 2004, 2009);

1) Uncertainties in hazard identification aiming at the identification of potential adverse effects associated with exposure to the agent. Data of toxicity tests (single dose toxicity tests, repeated dose toxicity tests, reproductive and developmental studies and genotoxicity tests) are used in this step.

2) Uncertainties in hazard characterization relating to the qualitative and quantitative evaluation of the adverse

effects associated with exposure to the agent. Animal data derived from dose-response studies, toxicokinetic studies and mechanical studies are used to predict adverse effects of the agent in human.

3) Uncertainties in exposure assessment indicating the qualitative and quantitative evaluation of the intake (daily intake, duration of intake, mode of intake), distribution, metabolism, excretion, and their specific differences. Characteristics of exposed population such as population with large amount of intake or population of high susceptibility are examined in this step.

4) Uncertainties in risk characterization being the final step to integrate hazard identification, hazard characterization and exposure assessment into an estimation of the adverse effects occurring in a target population.

Risk characterization for the agent gives practically an answer to the questions regarding to (1) A level of exposure considered to present minimal or no risk for health effects (LOAEL: lowest observed adverse effect level to NOAEL: no observed adverse effect level extrapolation), (2) Possibility of an appearance of reaction and its mechanism in human, and (3) Relationship between dose (or intake) and toxic degree in human (dose-response relationships).

To minimize or reduce uncertainties in risk analysis, hazard characterization is available for final risk analysis. An introduction of genotoxic data into evaluation of carcinogenic risk assessment is cited as an example. As other instance, corrections of a safety factor or uncertainty factor for establishment of the acceptable daily intake/tolerable daily intake (ADI/TDI) and the reference dose/reference concentration (RfD/RfC) are tested by using data from in vivo kinetics (absorption, distribution, metabolism, excretion) and knowledge of reaction mechanism (IPCS, 2009).

In the WHO/IPCS guidance (2012), considerations in the application of uncertainty factors for immunotoxicity data are individually presented as uncertainty factors of intraspecies, interspecies and database (in some instances, adding matrix factor, use and time factor) for immunosuppression, immunostimulation, sensitization (allergic response) and autoimmunity. However, the application of each uncertainty factor is too insufficient to be good predictors for subsequent clinical data or epidemiological studies so far.

Immunotoxicity Risk Assessment for Chemicals

In the 1974, from a standpoint of preventive medicine, the author began to feel keenly the necessity of the risk

assessment to evaluate individually the toxicity of such main biofunction as brain-nerve function, immunofunction and endocrine function. First, the author began to aim at systematizing and giving each toxicological science an assured status, and further advocated each as brain-neurotoxicology, immunotoxicology, and endocrinotoxicology. These denominations and concept of biofunctional toxicology in the 1974 are the first in Japan.

Of each toxicological science, immunotoxicology has made great advancements ever since. Currently, immunotoxicology is recognized as a mature sub discipline of toxicology, and has reached the state at which information on hazard can be applied to risk assessment with the careful consideration of available guidance.

Up to now, there are the two major international guidance documents on immunotoxicity risk assessment: One is ICH S8 Guideline for human pharmaceuticals and the other is the IPCS/WHO Guidance for chemicals.

In March 2012, the World Health Organization (WHO)/International Programme on Chemical Safety (IPCS) provide a harmonized guidance for immunotoxicity risk assessment for chemicals (Guidance for Immunotoxicity Risk Assessment for Chemicals, 2012). The WHO guidance presents how information obtained by immunotoxicity assessment may be applied for risk assessment in the population. This guidance is the first document published as immunotoxicity risk assessment for chemicals up to now.

The aim of the WHO/IPCS harmonization project document is to facilitate international harmonization of immunotoxicity risk assessment, that is to say, to harmonize global approaches to chemical risk assessment, including by increasing knowledge and agreement on basic risk assessment principles; developing international guidance documents on specific issues; and enhancing the practical use of risk assessments globally.

The guidance states that immunotoxicity risk assessment should be performed according to the same principal approaches as applied in risk assessment for other toxicological end-points, because the immune system or each type of immunotoxicity manifests many special aspects that need specific consideration in risk assessment. Furthermore, the guidance recommends that a weight of evidence approach is most suited for risk assessment of immunotoxicity, and that the approach should include clinical and epidemiological information, equally as information from animal experiments and other information.

Immunotoxicity risk assessment of chemicals is an evaluation of the potential for unintended effects of chemical

exposure on the immune system. These effects manifest as following principal types of immunotoxicity: immunosuppression involving infection and carcinogenesis etc, immunoaccentuation involving sensitization and autoimmunity, or immunostimulation. Such immune dysregulation may lead to many different types of illnesses. Included among them are illnesses that are associated with a dysfunctional immune system, such as infections, inflammatory diseases, allergic diseases, autoimmune diseases, etc, although all of them are not induced by chemical exposure.

For instance, exposure to xenobiotics is associated with immunosuppression manifesting the reduction of resistance to infections, development of autoimmune disease and hypersensitivity responding directly as allergen or enhancing the induction of allergic sensitization. Risk associated with immunostimulation is relatively difficult of the determination.

With the latest advance of immunology, a number of novel immunocompetent cells that play a part in the regulatory mechanisms of cellular immunity, humoral immunity, inflammation and autoimmunity are being found out through characteristic analysis. They include T cell subsets such as Th1, Th2, Th17, Tfh, Treg, NKT, macrophage and dendritic cell. Furthermore, the advance in immunology is producing new knowledge about findings of pattern recognition receptors responsible for innate immunity such as TLRs, RIG-1Rs, NLRs, dectin-1; and further about the regulation of immune system cell differentiation and immune response by nuclear receptors including AhR, PPARs, RARs, RXR, RORs, GR and VDR. As the latest knowledge, there are miRNA and epigenetic factors that play important roles in gene regulation, and introduction of “omics” techniques into immunotoxicology.

Thus, the up-to-date knowledge and information on novel cells and functional molecular in immunity, which are increasing and accumulating by leaps and bounds, have raised awareness that they should/must be comprehensively surveyed, regulated and applied to immunotoxicology and further immunotoxicity risk assessment, although such processes are complicated.

Unfortunately, however, the current application is insufficient in the practical stage of clinical and environmental immunotoxicity risk assessment. Especially in clinical

field, there is currently a lack of adequate standardization for immune monitoring tests during clinical trials in immune safety issues and a lack of specific immunotoxicity biomarkers to improve the immune-safety of chemical agent. Most of means used for clinical immunotoxicity risk assessment are those for immunosuppression, and there is little reference to the assessment of immunostimulatory and immunomodulatory compounds, because of lack of the good risk assessment models for detecting their compounds that can translate to clinical risk assessment.

Therefore, there is a need to identify the current state and quality of the science assessing risk assessment models for immunomodulatory effects or immunostimulatory effects in the principal types of immunotoxicity as described above, as well as a need to identify research gaps and to update the current guidance.

From these points of view, regulatory science is an indispensable discipline to improve the quality of the immunotoxicology and further immunotoxicity risk assessment, and also to give each immunotoxicological science an assured status.

Particularly, under the existing conditions being flooded with uncertainty, it is important that the up-to-date knowledge in immunology and toxicology is applied to immunotoxicology and immunotoxicity risk assessment, and the uncertainty of scientific knowledge is complemented, and further public consensus is gained on the basis of a theoretical concept and an adequate judgment in regulatory science.

Conclusion

The first guidance has been just defined for immunotoxicity risk assessment for chemicals (WHO/IPCS, 2012), but it admits of no doubt that it is insufficient in the level of practical application. It is not till now for the author to feel that immunotoxicity risk assessment may be started along the right lines. After this, it is necessary that accumulating useful scientific products will be comprehensively surveyed and adequately assessed for subsequent decision-making from the standpoint of regulatory science so as to be able to contribute toward society.

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