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FDA Research in Regulatory Risk Assessment

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ABSTRACT

The responsibility of the United States Food drugs and Drug Administration (FDA) is to assure the safety of foods, drugs and cosmetics. To fulfill its mandated mission, FDA has to carry out research in order to improve testing technology and risk assessment. The National Center for Toxicological Research (NCTR) is currently carrying out research in support of this mission. This paper briefly describes regulatory risk assessment research at the NCTR.

Key words : Regulatory risk assessment, National Center for Toxicological Research, Regulatory research, Chloral hydrate.

INTRODUCTION

The assurance of safety of foods,human and animal drugs, cosmetics, biological products, radiation-emitting electronic products,and medical devices in interstate commerce is the responsibility of the Food and Drug Administration (FDA) of the United States. To fulfill its mandated mission, the FDA has to carry out research in order to improve testing technology and risk assessment. In the preceding paper, Dr. Chiu S. Lin addressed the U. S. FDA regulatory procedures and guidelines for ensuring product safety. To ensure the safety of products, most of the FDA's Centers are involved in research in regulatory risk assessment. For example, the Center for Food Safety and Applied Nutrition (CFSAN) has the responsibility for maintaining and improving the safety, wholesomeness and nutritional quality of the national food supply. Scientific research will enable CFSAN to maintain and improve risk assessment and prevent foor-borne injury and disease. The Center for Devices and Radiological Health (CDRH) has the responsibility for controlling unnecessary exposure of humans to ionizing and nonionizing radiation-emitting electronic products.

The National Center for Toxicological Research (NCTR) has been the FDA's major research Center for supporting the mission of the FDA. Currently, the FDA already has plans to increase the utilization of NCTR's expertise and facility to support FDA's regulatory research. Intensive collaborative research between NCTR and the other FDA Centers has been established. Thus, NCTR is carrying out a major role in performing regulatory risk assessment for FDA. In this paper, we describe the major regulatory research at the NCTR.

RISK ASSESSMENT AND RISK MANAGEMENT

There are four steps in performing risk assessment; hazard identification, exposure assessment, dose-response assessment, and risk characterization. Hazard identification is to determine whether or not exposure to a chemical can cause an increase in the incidence of a health condition. Epidemiological studies, animal bioassays and structure-activity analyses are the major sources for obtaining data for hazard identification. Exposure assessment is the process of defining the quantity of a chemical that comes into contact with human population. The duration of exposure, magnitude of exposure into the body, route of exposure, and sensitivity of the population need to be determined and evaluated. Dose-response assessment is the process of estimating the relation between dose of an agent and the incidence of an adverse effect. Risk characterization if the process of integration of the data and analysis involved in the first three steps (e.g., hazard identification, exposure assessment, and dose-response assessment) to determine the likelihood the chemical poses a human hazard. Risk management combines the risk assessment with the directives of regulatory legislation, together with socioeconomic, technical, political, and other considerations, to reach a decision as to whether or how much to control future exposure to the suspected toxic substance.

Regulatory research in risk assessment is very difficult. By definition, "risk" indicates the probability of an adverse health effect resulting from exposure to a hazardous chemical or a mixture of substances. The adverse health effects are the biological result of exposure to naturally occurring or the man-made toxicants. These biological effects include: cancer, reproductive problems, genetic effects, clinical effects and subclinical effects. While the clinical and subclinical effects can be easily evaluated, the causes of cancer induction, reproductive problems, and genetic effects are usually much more difficult to be detected and assessed. Because of the history of methodological development, emphasis has been placed on risk assessment for carcinogenesis. Recently, the other end points such as teratogenesis, mutagenesis, neurotoxicity, and immunotoxicology are also considered.

To perform risk assessment for carcinogenesis is highly challenging. Isolation, identification, and quantification of toxic chemicals that we are exposed to are not easy. Accurate assessment of carcinogenic potency of a chemical is very difficult also. Production of tumors in an animal species does not prove that the chemical is a human carcinogen. Also, failure to produce tumors in animals does not eliminate the possibility that the chemical would be carcinogenic in man. There exist a large number of uncertainties concerning the use of experimental animal data for interpretation of human health risk posed by carcinogenic chemicals. Furthermore, because most of the carcinogenic chemicals require metabolic activation, risk evaluation must be based on the quantitative estimate of the dose of the reactive metabolites delivered to the target tissues, and based on the carcinogenic potency of the metabolites. Without sufficient knowledge, uncertainties (assumptions) are introduced into the risk assessment process that allow wide interpretation of the limited experimental data that are available. As a consequence, it is important to pursue critical data on the relationship between exposure, dose to target tissue (delivered dose), and associated health effects. Emphasis is on the laboratory and field research to improve understanding of basic biological mechanisms, especially as they relate to our ability to extrapolate from one set of circumstances to another and will allow us to quantify the human health risks associated with human exposures.

REGULATORY RESEARCH AT THE NATIONAL CENTER FOR TOXICOLOGICAL RESEARCH (NCTR)

The NCTR was founded in 1972, and historically has been a research agency designed for conducting chronic and subchronic toxicological studies. Since the National Toxicology Program (NTP) was founded in 1978, NCTR has been

actively linked to this Program, including on-site subchronic and chronic bioassays. Such long term bioassays have had significant contribution on the FDA's regulatory assessment of several human and animal drugs, such as gentian violet, sulfamethazine, and doxylamine. To efficiently serve FDA's research needs in accordance with its current and future regulatory functions, research has also been emphasized on the understanding of the biological mechanisms underlying the toxicity of products regulated by the agency. Accordingly, the NCTR has been refocused into nine programmatic areas. As described in the "NCTR Ongoing Research", "Currently each of the projects is directed toward the resolution of regulatory issues, the solution of which will be expected to provide the scientific understanding for regulatory decision making." This unique approach will enable FDA to perform risk-benefit assessment in a much more efficient and reliable manner. In order to efficiently perform regulatory risk assessment for FDA, intensive collaborative research between NCTR and the orther FDA's Centers has been established.

The goals and the significance to FDA of these nine programs are briefly described below:

1. Analytical Methods Developmental Program - To develop and validate rapid, sensitive, and reliable analytical methodologies for enforcement of regulations governing adulterants, contaminants, composition, and potencies in FDA regulated products.

2. Applied and Environmental Microbiology Program - To determine the role of intestinal microflora in the activation or detoxification of xenobiotics; and to employ microorganisms as models to predict the metabolic pathways by which drugs are metabolized in mammals.

3. Biochemical and Molecular Markers of Cancer Program - To improve and conduct subchronic and chronic toxicological bioassays to address the FDA's regulatory needs, and to develop new approaches, such as biomarkers, to increase the sensivity in performing risk assessment.

4. Developmental Toxicology Program - To improve methods for detection and prediction of developmental toxicity in the human population, to elucidate the mechanisms of developmental toxicant effects, and to improve biologically-based dose-response models for developmental risk assessment.

5. Neurotoxicology Program - To develop and validate quantitative biomarkers of neurotoxicity, to utilize the developed biomarkers to elucidate mechanisms, and to enhance the certainty of assumptions underlying risk assessment of neurotoxicants.

6. Nutritional Modulation of Risk and Toxicology Program - To determine the mechanisms by which dietary constituents affect the toxicological effects of chemicals, and based on the findings, make appropriate recommendations to FDA and other regulatory agencies.

7. Quantitative Risk Assessment Program - To conduct mathematical research to improve current statistical procedures for quantitative risk assessmemt.

8. Solid-State Toxicity Program - To determine the mechanisms of long-term toxicity of implanted materials, and provide scientific information for FDA's regulatory decision.

9. Transgenic Program - To develop and validate sensitive and predictive transgenic human *in vitro* systems and rodent *in vitro* and *in vivo* systems for identifying and quantifying human toxicants.

Carcinogenesis is the major concern on risk assessment. Thus, two representative research "areas" on carcinogenesis that are currently being carried out at the NCTR are described below. The first research area is to integrate the

elucidation of mechanisms to the study of subchronic and chronic bioassays, and the second research area is to develop and validate biomarkers as surrogates to increase the sensitivity in performing risk assessment.

I. *Toxicology and Carcinogenicity Study Program*

As described earlier, subchronic and chronic bioassays have had significant contribution on the FDA's regulatory assessment. To fully utilize and strengthen the expertise and facility, the NCTR and the National Institute of Environmental Health Sciences (NIEHS), cooperating member agencies of the National Toxicology Program, recently established an agreement to development of a scientific database on substances of particular interest to the FDA, with special emphasis on: (i) reduction of the uncertainty in risk-assessment and risk-benefit analyses; (ii) provision of a better estimate of true risk leading to high-quality, science-based risk management decisions; and (iii) development and application of carcinogenicity study designs that best meet the regulatory needs of the FDA. The first compound that this Program studied was chloral hydrate. In performing FDA's regulatory toxicological assessment on chloral hydrate, presently, the Biochemical and Molecular Markers of Cancer Program, the Transgenic Program, and the Nutritional Modulation of Risk and Toxicology Program are participating. Four approved protocols will determine: (i) the mechanisms by which chloral hydrate exert its genetic toxicity; (ii) range-finding toxicity of chloral hydrate in male and female $B6C3F_1$ mice; (iii) range-finding toxicity ofchloral hydrate in male and female F344 rats; and (iv) following briefly describes the background of chloral hydrate and the approaches to determine its mechanism(s) of toxicity.

(I). *Background of chloral hydrate*

Chloral hydrate has been in use as a hypnotic and sedative since the nineteenth century. Although it has adverse gastrointestinal effects, chloral hydrate is still being widely used as a sedative for children's dentistry and has other medical uses involving minor surgery and diagnostics. This compound has been used as a sedative and anesthetic for horses, cattle, swine, and poultry. In addition, chloral hydrate has been identified by the U.S. Environmental Protection Agency as a product of the water chlorination process. Chloral hydrate was reported gy Daniel *et al.* in *Fundamental and Applied Toxiciology* in 1992 to induce hepatic neoplasms. It induced 71% (17/24) liver adenomas or carcinomas to male $B6C3F_1$ mice exposed to levels of 1g/L chloral hydrate, or 166 mg/kg/day of chloral hydrate, via the drinking water for two years; while the control animals treated with the vehicle, distilled water, developed 15% (3/20) liver adenomas or carcinomas.

(II). *Determination of the mechanism of chloral hydrate*

The approaches to determine the mechanism of chloral hydrate leading to genotoxicity are as follows:

1. To characterize and quantify the metabolites of chloral hydrate formed from *in vitro* metabolism of chloral hydrate by liver microsomes, mitochondria, and cytosols of $B6C3F_1$ mice, F344 rats, and humans;

2. To determine the mechanism of metabolic activation of chloral hydrate leading to mutations by determining the mutagenicity of chloral hydrate and its metabolites in *S. typhimurium* tester strain TA100 with S9;

3. To prepare synthetically carcinogen-modified DNA adduct(s) of chloral hydrate and its metabolites, and to characterize and quantify the DNA adducts formed *in vitro* (incubation in the presence of calf thymus DNA) and *in vivo*;

4. To determine the principal metabolizing enzymes responsible for metabolic activation and DNA binding of chloral hydrate and its metabolites in mice, rats and humans; and

5. To study mutagenicity, metabolism and DNA adduct formation of chloral hydrate and

its metabolites in transgenic human lymphoblastoid cells expressing cytochrome P-450 (CYP) 2E1 and other CYP's, and to determine which (if any) human CYP isozyme is the principal enzyme responsible for metabolic activation of chloral hydrate.

II. *Biomarkers*

Biomarkers are potential surrogates for human health risk assessment. It can also provide information concerning the mechanisms by which the toxic chemicals exert their adverse activities, including carcinogenicity, in humans. Biomarkers can monitor human exposure and effect of a toxic component present in the food chain, drugs, or in the environment. Thus, it is anticipated that development of sensitive biomarkers for risk assessment will be one of the major research areas in medical science and in regulatory research. An ideal biomarker to be developed should be non-invasive and interpretable in terms of human susceptibility to exposure of effect. DNA adducts will be the critical biomarkers to measure the effect of a carcinogenic chemical to human health. Nevertheless, although several modern techniques have been employed successfully to identify and quantify DNA adducts, all encounter different types of problems. The most important problem is detection capability. It is important to improve the current analytical methodologies and to develop new methodologies for accurate detection and quantification of DNA adducts, protein adducts and other biomarkers. Currently, there are a number of on-going research projects under the Biochemical and Molecular Markers of Cancer Program to study DNA and protein adducts as biomarkers. Some of these research projects and their goals are listed below:

1. Several food pyrolysates have been found to be highly tumorigenic in experimental animals. A protocol has been initiated to detect the DNA adducts derived from these food pyrolysates in humans. Among these food pyrolysates, 2-amino-1-methyl-6-phenylimidazo[4,5-b] pyridine (PhIP) is a blood-borne carcinogen, and has been detected in fried beef. Another protocol is to determine the metabolic activation pathways and DNA adducts of PhIP, and to develop sensitive methodologies for detecting its DNA adduct(s) in performing risk assessment.
2. 3'-Azidothymidine is an anti-HIV drug. However, it is also a carcinogen. A protocol is underway to determine its mechanisms for the carcinogenicity and to study the incorporation of this drug into DNA of target tissues.
3. Urethane has been found as a food-borne carcinogen. In collaboration with CFSAN, a protocol is proposed to characterize its DNA adducts and to develop sensitive methods for detecting these adducts.
4. The analgesic drug, acetaminophen, exhibits liver toxicity. Currently, a protocol will employ an immunochemical method to detect the acetaminophen-induced protein adducts as a biomarker of toxicity in humans.
5. As described earlier, the NCTR is studying the genotoxicity of chloral hydrate. This study also includes whether or not its DNA adducts, if formed, are relevant biomarkers.
6. A protocol determines the role of arylamine acetylation and N-oxidation phenotypes in human urinary bladder, colorectal, and lung cancer.
7. Mass spectrometry is one of the most promising methodologies for detection of DNA adducts in a tiny quantity. A protocol is being conducted to improve the sensitivity of this technology in detecting different classes of toxicologically significant compounds, including polycyclic aromatic hydrocarbons (PAHs), nitrated PAHs, arylamines, and food pyrolysates.

PERSPECTIVES

Recently, FDA's strategic plan for future lists regulatory science as the second highest priority. The Commissioner of FDA, Dr. David Kessler, has pointed out the importance of re-

gulatory research and emphasized that "when we discuss significant scientific and regulatory matters, it is important to bring a scientist to the table-someone who can analyze the issue and evaluate the arguments-all of this with a scientist's particular point of view," and that "science drives policy-make FDA's policy judgements much more than simply one person's opinion against another's." Regulatory research is timely and important. FDA has a major regulatory responsibility and consequently employs risk assessment and risk management to meet this responsibility. We anticipate that regulatory research at FDA will significantly help improve quantitative risk assessment which currently we encounter with difficulty.

美國食品藥物管理署的毒性物風險評估研究

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摘　　要

美國食品藥物管理署負有確保食品、藥物及化粧品安全的任務。爲了盡善其職，必須做毒性物風險評估的研究，祈能在風險評估的技術上，精益求精。所屬的美國國家毒理研究中心，主要的任務，便是進行風險評估的研究，本文在此簡介該研究中心的工作。

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