

Features of the organization for priority decision on test substances under chronic inhalation carcinogenic toxicity testing approach

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허용, 김창열, 박정은, 임경동

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차신우, 허용주, 최성진, 김용재, 표지훈, 최수현, 전도인, 유동현, 강미현

안전성평가연구소

윤진하

연세대학교 의과대학

본 연구는 한국산업안전보건공단 "산업화학물질 만성발암성평가 체계 구축을 위한
만성흡입독성시설 활용 방안" 용역 연구과제 일부로 수행되었음

Lesson from the History

I. National Toxicology Program of the United States

1. Background reason for the establishment at 1978

- 주로 발암성 시험 관련 기관간 시험 협력 체계 부재를 해결하기 위함
(US. Department of Health, Education, and Welfare, Public Health Service.
Establishment of a National Toxicology Program. Federal Register 43:53060)
- 발암성시험 소관 업무 : 1981년 부터 NCI에서 NTP로 이전
(NCI는 기초연구 기관으로서 routine toxicology testing을 수행하지 않게 됨.
발암성 시험 비용의 대부분 (87%)은 NIEHS에서 지원)
- 1981년 상시 조직으로 승인됨

2. Member agencies at the time of 1978 establishment

- NIH 산하 NCI, NIEHS
- CDC 산하 NIOSH
- FDA 산하 NCTR

3. Configuration on US organizations with toxicology disciplines

Department of Health and Human Services

NIH INSTITUTES

- **National Cancer Institute (NCI)**
- National Eye Institute (NEI)
- National Heart, Lung, and Blood Institute (NHLBI)
- National Human Genome Research Institute (NHGRI)
- National Institute on Aging (NIA)
- National Institute on Alcohol Abuse and Alcoholism (NIAAA)
- National Institute of Allergy and Infectious Diseases (NIAID)
- National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)
- National Institute of Biomedical Imaging and Bioengineering (NIBIB)
- *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD)
- National Institute on Deafness and Other Communication Disorders (NIDCD)
- National Institute of Dental and Craniofacial Research (NIDCR)
- National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
- National Institute on Drug Abuse (NIDA)
- **National Institute of Environmental Health Sciences (NIEHS)**
- National Institute of General Medical Sciences (NIGMS)
- National Institute of Mental Health (NIMH)
- National Institute on Minority Health and Health Disparities (NIMHD)
- National Institute of Neurological Disorders and Stroke (NINDS)
- National Institute of Nursing Research (NINR)
- National Library of Medicine (NLM)



Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

- **National Institute for Occupational Safety and Health**
- Office for State, Tribal, Local and Territorial Support
- Office of Equal Employment Opportunity
- Office of Infectious Diseases
 - National Center for Emerging and Zoonotic Infectious Diseases
 - National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
 - National Center for Immunization and Respiratory Diseases
- Office of Minority Health and Health Equity
- Office of Noncommunicable Diseases, Injury and Environmental Health
 - National Center for Chronic Disease Prevention and Health Promotion
 - National Center for Environmental Health **Agency for Toxic Substances and Disease Registry**
 - National Center for Injury Prevention and Control
 - National Center on Birth Defects and Developmental Disabilities
- Office of Public Health Preparedness and Response
- Office of Public Health Science Services
 - Center for Surveillance, Epidemiology and Laboratory Services
 - National Center for Health Statistics



United States Environmental Protection Agency

[National Center for Computational Toxicology](#)

[National Center for Environmental Assessment](#)

[National Center for Environmental Research](#)

[National Exposure Research Laboratory](#)

[National Health and Environmental Effects Research Laboratory](#)

[National Homeland Security Research Center](#)

[National Risk Management Research Laboratory](#)



U.S. Food and Drug Administration
Protecting and Promoting *Your Health*



Food and Drug Administration
NCTR
National Center for Toxicological Research



**UNITED STATES
DEPARTMENT OF LABOR**

OSHA

Occupational Safety & Health Administration

4. Committees under NTP at 1980

❖ Steering Committee (운영위원회)

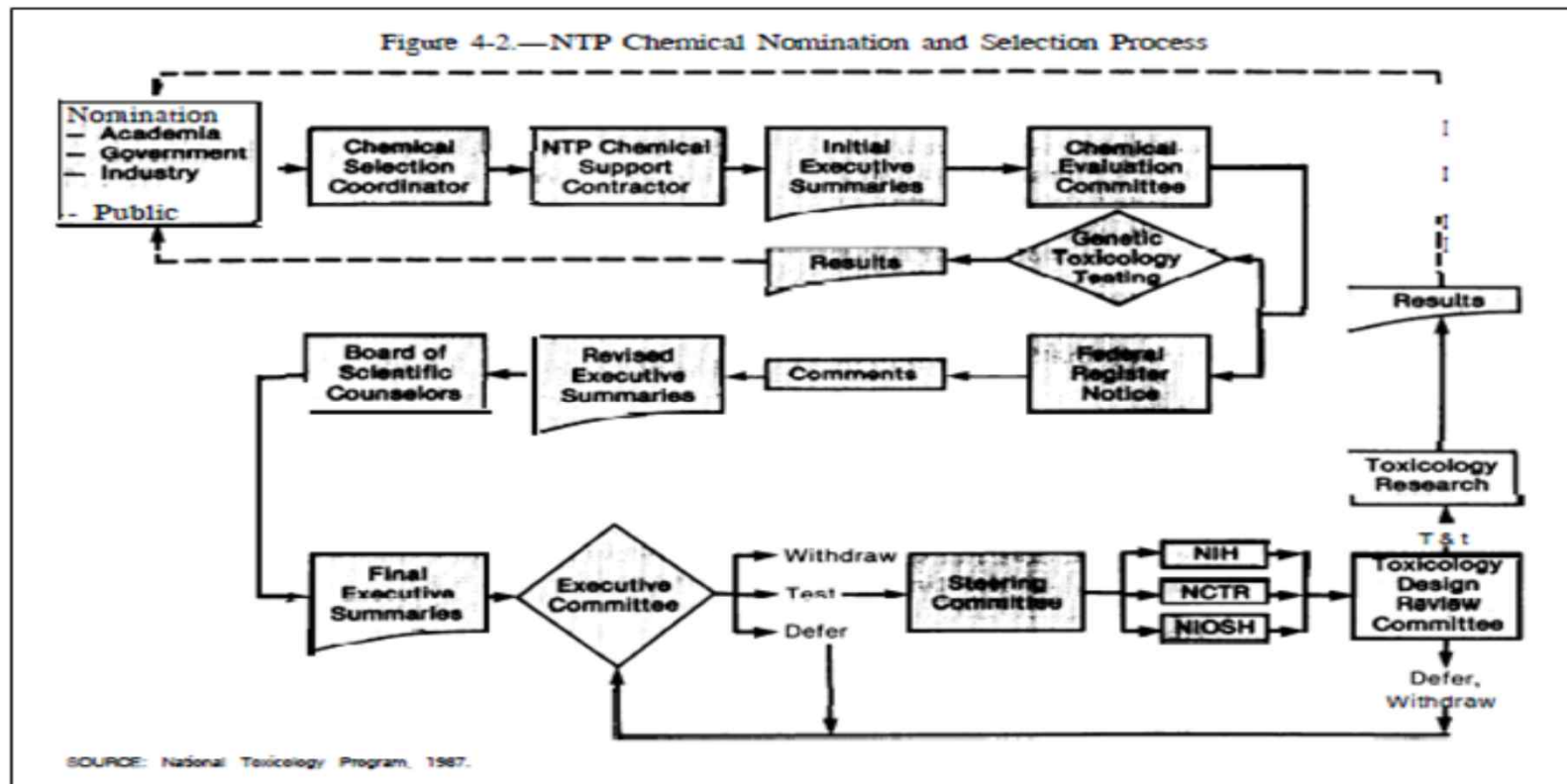
- Directors of NIEHS, NIOSH, NCTR
- 기관간 협력상 현안 해결, 기관간 발암성 시험 물질 배분 결정 등
- 년 3 ~ 4회 정례회의
- 실행위원회에서 선정한 시험 물질들에 대한 상기 3개 기관 배분. 해당 기관에서는 시험 protocol 개발하여 "Toxicology Design Review Committee에 제출.

❖ Executive Committee (실행위원회)

- Directors of EPA, FDA, OSHA, CPSC (Consumer Product safety Commission) :
자문위원회를 거치지 않고 물질 제안 가능 (1 물질/년/기관)
- Directors of NIH, NIEHS, NCI, NIOSH
ATSDR (1987년 투표로 포함 결정)
- Dept. Health and Human Services 차관 (non-voting member)
- NCTR (nonvoting consultant)
- NTP 년차별 계획 승인 (**시험물질 순위 결정 및 시험 기관 조율**)
및 모니터링 등 (**최종 시험물질 선정함**)
- 년 3 ~ 4회 정례회의를 통해 시험 계획안 평가, 시험법 추천
(추천 시험물질은 Federal Register에 2개월간 공공 의견 수렴)

❖ Board of scientific counselors (자문위원회)

- Dept. Health and human Services에서 8인 전문가 추천
- 공공 의견 수렴 보고서에 대한 검토를 통해 시험 우선 순위 등 자문 의견 취합 실행 위원회 전달
- 년 3 ~ 4회 정례회의



5. Chemical selection principles of NTP

원칙 : 정부가 지정하는 GLP 기관에서 기업 부담으로 시험해야 함

table 4-2.—NTP Chemical Selection Principles^a

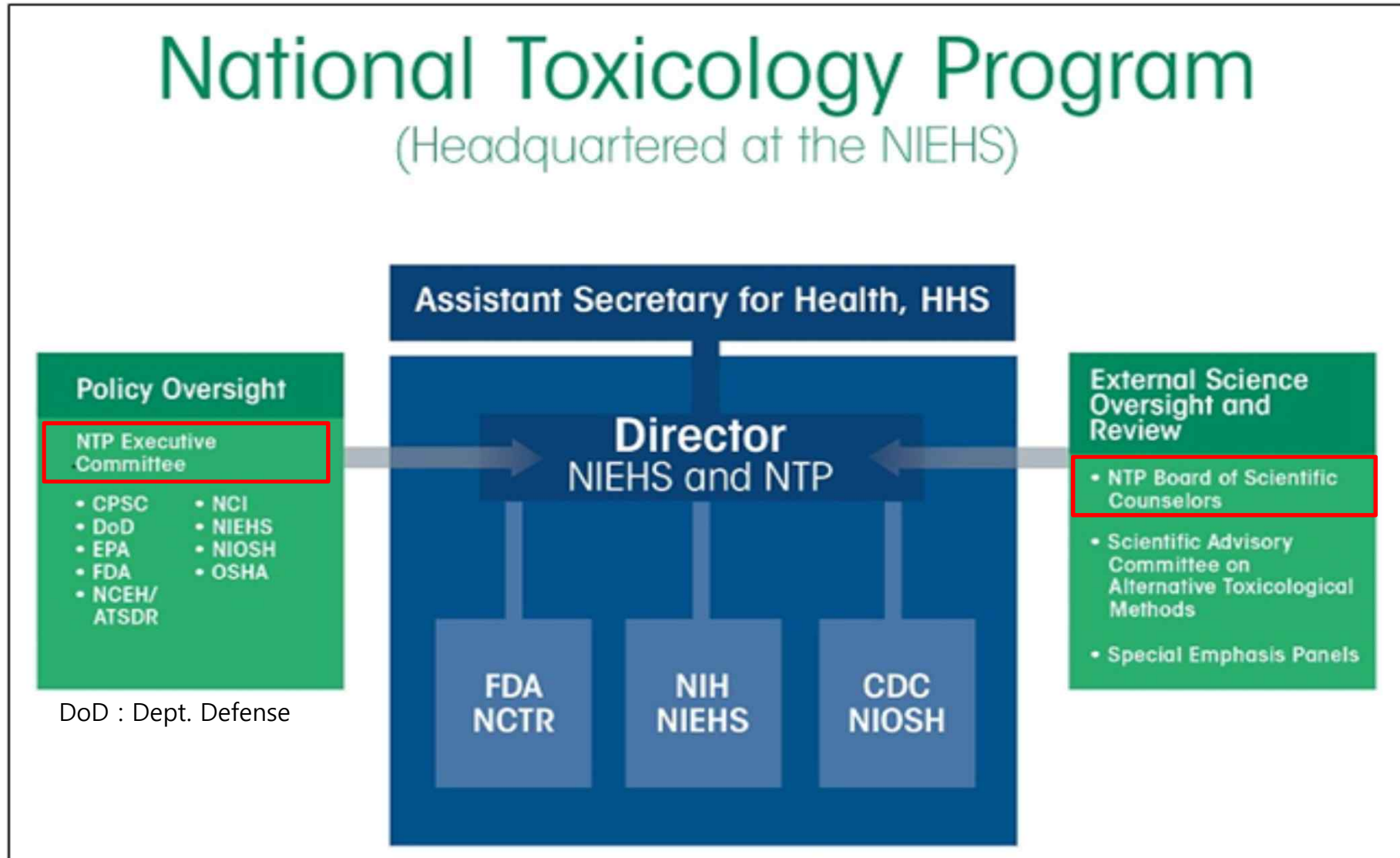
1. Chemicals found in the environment that are not closely associated with commercial activities (1 1);
2. Desirable substitutes for existing chemicals, particularly therapeutic agents, that might not be developed or tested without Federal involvement (1);
3. Chemicals that should be tested to improve scientific understanding of structure-activity relationships and thereby assist in defining groups of commercial chemicals that should be tested by industry (91);
4. Certain chemicals tested by industry, or by others, the additional testing of which by the Federal Government is justified to verify the results (27);
5. Previously tested chemicals for which other testing is desirable to cross-compare testing methods (8);
6. "Old chemicals" with the potential for significant human exposure which are of social importance but which generate too little revenue to support an adequate testing program (some of these may be "grandfathered" under FDA laws) (15);
7. Two or more chemicals together, when combined human exposure occurs (such testing probably cannot be required of industry if the products of different companies are involved) (1); and
8. In special situations, as determined by the Executive Committee, marketed chemicals which have potential for large-scale and/or intense human exposure, even if it may be possible to require industry to perform the testing (39).

^aNumbers in parentheses indicate the number of times the principle was used to support a CEC recommendation for testing in animals.

SOURCE: National Toxicology Program

U.S. Department of Health, Education, and Welfare, National Toxicology Program. Board of Scientific Counselors, Report of the NTP *Ad Hoc* Panel on Chemical Carcinogenesis Testing and Evaluation. Research Triangle Park, NC, 1984

6. Chemical selection principles of NTP at the present days



❖ Multi-step nomination process for carcinogenic study

1) Receipt and initial review

- Nominations are reviewed by the NTP Office of Nominations and Selection to determine whether the substance has been adequately tested or has been previously considered by NTP.
- For nominations not eliminated from consideration or deferred at this stage, the available information on the substance is examined in detail to prepare a Chemical Information Review Document that summarizes the relevant data for each substance.

2) Development of research concepts

- To facilitate review of nominations by the NTP Board of Scientific Counselors (BSC) and the public, NTP staff develop draft research concept documents for each nomination : A research concept is a brief document outlining the nomination or study rationale, and the significance, study approach, and expected outcome of a proposed research program tailored for each nomination.
- The purpose of these research concept documents is to outline the general elements of a program of study that would address the specific issues that prompted the nomination, but also encompass studies that may address larger public health issues, or topics in toxicology that could be appropriately addressed through studies on the nominated substance or issue. Interagency review is invited.

❖ Multi-step nomination process for carcinogenic study

3) NTP Board of Scientific Counselors

- Nomination supporting documents, draft research concept documents, and any public comments received on the nominations are then presented to the NTP Board of Scientific Counselors for review.
- The public meeting also provides an opportunity for NTP to receive additional public comments.
- The Board suggests additional studies as well as offer their perspective on issues raised by public comments.

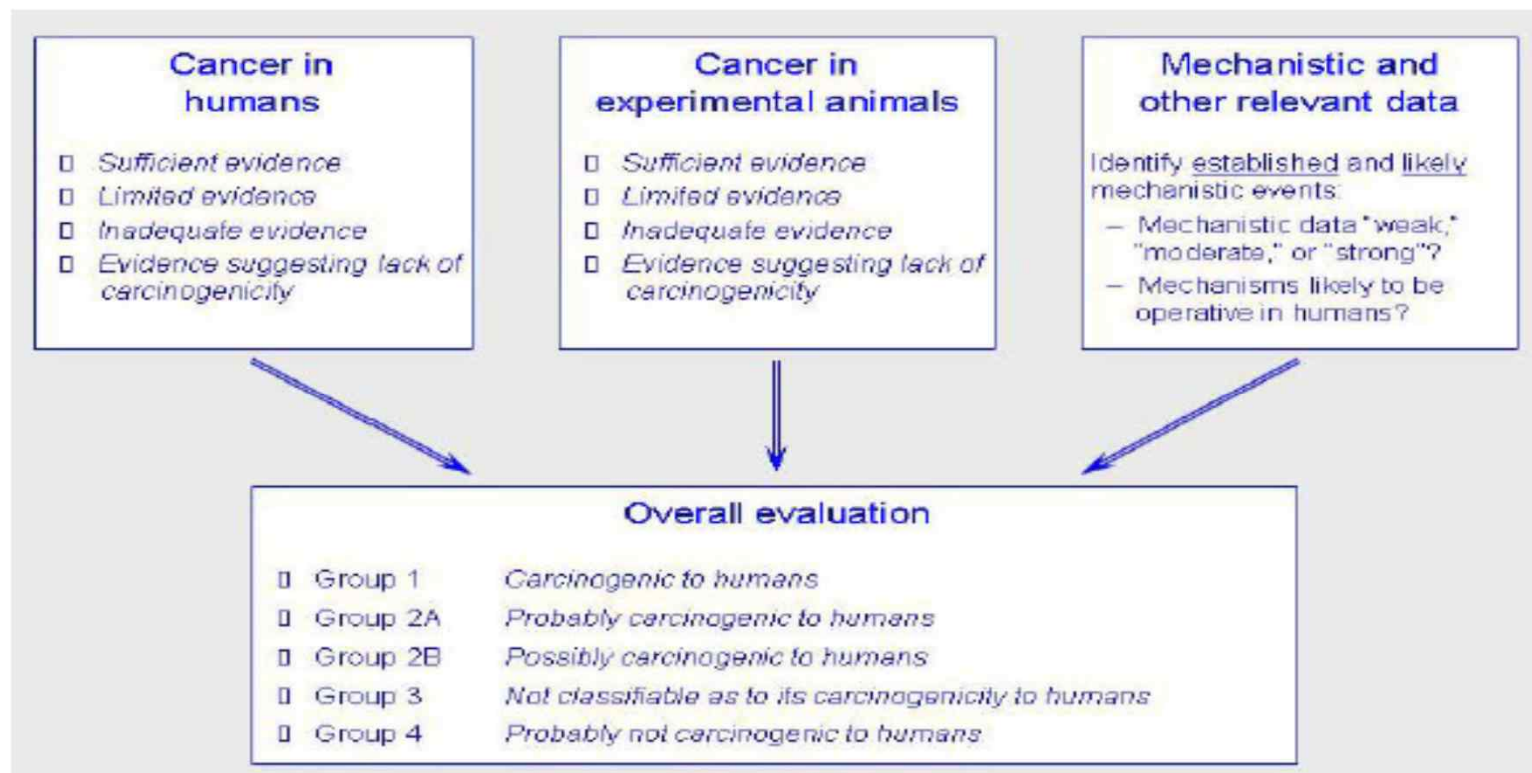
4) Implementation of study recommendations

- Each nomination selected for study is assigned to an NIEHS, FDA, or NIOSH staff scientist (project leader) who assesses the information compiled during the nomination review and selection process and other pertinent current information.
- Project leaders then assemble a Study Design Team composed of staff from NTP, NIEHS, and other government agencies to formulate a detailed study plan.
- If a study is warranted, the project leader presents a detailed study proposal to an NIEHS/NTP Project Review Committee. All studies approved as a result of this process are then implemented as time and resources permit.

II. International Agency for Research on Cancer (IARC)

1. IARC 발암성 물질에 대한 Monograph 작성 최근 동향

- IARC Technical Publication No. 42: Identification of research needs to resolve the carcinogenicity of high-priority IARC carcinogens에 근거함
- Group 2A, 2B 에 있는 suspected carcinogens에 대한 확실한 분류를 위한 노력 : 인체에 대한 노출 자료의 제한점을 극복하기 위하여 기전적인 근거를 응용대입.



EVIDENCE IN EXPERIMENTAL ANIMALS

Sufficient

Limited

Inadequate

ESLC

Sufficient

Group 1

Limited

↑1 strong evidence in exposed humans

Group 2A

↑2A belongs to a mechanistic class where other members are classified in Groups 1 or 2A

Group 2B (exceptionally, Group 2A)

EVIDENCE
IN HUMANS

Inadequate

↑1 strong evidence in exposed humans

↑2A strong evidence ... mechanism also operates in humans

Group 2B

↓3 strong evidence ... mechanism does not operate in humans

↑2A belongs to a mechanistic class

↑2B with supporting evidence from mechanistic and other relevant data

Group 3

↑2A belongs to a mechanistic class

↑2B with strong evidence from mechanistic and other relevant data

Group 3

Group 3

↓4 consistently and strongly supported by a broad range of mechanistic and other relevant data

ESLC

Group 3

Group 4

2. IARC 발암성 물질에 대한 Monograph 작성 과정

IARC, NIOSH, NIEHS, NCI, American Cancer Society 참여 (Working Group)

- 1) Working group회의 1년전에 IARC 직원들 및 전문가 그룹에 의해 검토 물질 리스트가 마련됨.
- 2) 이후 관련된 모든 자료 (출판 자료, CANCERLINE, MEDLINE, TOXLINE 등에서) 수집 : IARC 직원. 출판이 완료되었거나 게재 승인된 자료만 검토 대상이 됨.
- 3) SRI International, Stanford, CA에서 1차로 물리화학적 특성, 생산/제조, 암발생 및 관련 분석 자료를 종합하여 1차 초안 제작 (NCI와 IARC 계약에 의거함)---미국, 유럽, 일본 등의 자료 수집
- 4) Working group 회의 6개월전 1차 초안이 Working group 전 참가자들에게 의견조회를 위해 보내짐 :
Working group member들은 모든 자료가 수집되었는지 확인, 자료에 대한 요약, 실험연구 혹은 역학조사결과가 의미가 있는지 평가, 최종적으로 발암성 위험 평가하게 됨 (소속기관의 대표가 아닌 개인 전문가로서 자문함)
- 5) 회의는 Lyon에서 6~8일정도 실시. 토의를 거쳐 Monograph 최종 version 제작. 회의 6개월 후 완성본 출판함.

III. EU OSIRIS (유럽연합 국가간 협력 체제)

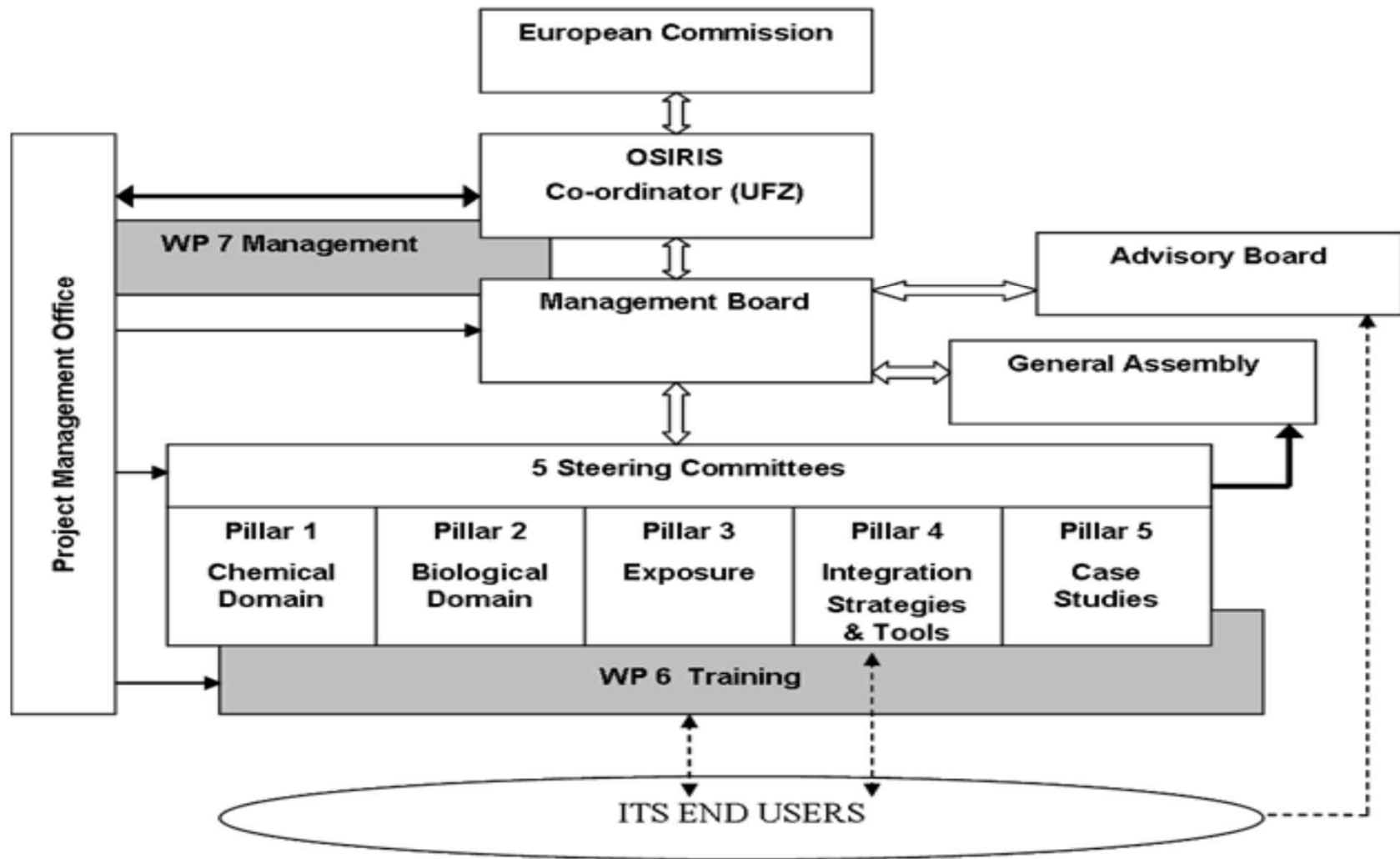
(Optimized strategies for risk assessment of industrial chemicals through integration of non-test and test information) : www.ufz.de/osiris



The OSIRIS Project (1 Apr 2007 – 30 Sep 2011)



	Helmholtz Centre for Environmental Research	UFZ	Leipzig, Germany	
	Universitat Rovira i Virgili	URV	Tarragona, Spain	
	Liverpool John Moores University	LJMU	Liverpool, United Kingdom	
	University of Berne	UB	Berne, Switzerland	
	National Institute of Public Health and the Environment	RIVM	Bilthoven, The Netherlands	
	Technical University of Denmark	DTU	Lyngby, Denmark	
	TNO Quality of Life	TNO	Zeist, The Netherlands	
	Istituto Di Ricerche Farmacologiche "Mario Negri"	IRFMN	Milan, Italy	
	Procter & Gamble, Company	P&G	Brussels, Belgium	
	Eidgenössische Technische Hochschule Zürich	ETHZ	Zurich, Switzerland	
	Istituto Superiore de Sanità	ISS	Rome, Italy	
	Universiteit Antwerpen	UA	Antwerp, Belgium	
	Vrije Universiteit Amsterdam	VU	Amsterdam, The Netherlands	
	Enginyeria de Sistemes, SME	SIMPPLE	Tarragona, Spain	
	KWR, Watercycle Research Institute	KIWA	Nieuwegein, The Netherlands	
	National Institute of Public Health	IVZRS	Ljubljana, Slovenia	
	National Institute of Chemical Physics and Biophysics	NICPB	Tallinn, Estonia	
	ECT Oekotoxikologie GmbH, SME	ECT	Flörsheim a.M., Germany	
	Fraunhofer-Institut für Toxikologie und Experimentelle Medizin	FhG	Hannover, Germany	
	Aarhus Universitet	AU	Aarhus, Denmark	
	Stockholm University	SU	Stockholm, Sweden	
	Bourgaz "Prof. As. Zlatarov" University	LMC	Bourgaz, Bulgaria	
	Merck KGaA, Company	MERCK	Darmstadt, Germany	
	Environmental Microbial Genomics Group - UMR CNRS 5005	CNRS	Lyon, France	
	Nofer Institute of Occupational Medicine	NIOM	Lodz, Poland	
	Joint Research Centre	JRC	Ispira, Italy	
	University of Exeter	UNEXE	Exeter, United Kingdom	
	Analytisches Laboratorium, SME	AL	Lohnstedt, Germany	
	DIALOGIK, SME	DIA	Stuttgart, Germany	
	Cyprotex PLC, SME	CYPROTEX	Macclesfield, United Kingdom	
	University of Wageningen	WUR	Wageningen, The Netherlands	



Goal : The goal of OSIRIS is to develop Integrated Testing Strategies (ITS) fit for REACH that make it possible to significantly increase the use of non-testing information for regulatory decision making, and to effectively reduce animal testing to the level needed from a risk perspective.

(만성흡입발암성시험 물질 우선 순위 결정시 ITS 전략을 병행해야할 것으로 판단됨)

Pillar 1: Chemical Domain

- Objective: To develop methods and guidance for transparent and scientifically sound use of chemistry-driven information in ITS.
- The methodology of Pillar 1 concerns all non-testing approaches that make use of **molecular structure information** for predicting fate and effect of chemical substances.

Pillar 2: Biological Domain

- Objective: To provide efficient strategies and guidance for exploitation of all types of biological information on toxic effects of chemicals in ITS, focusing on reduced animal use and informed extrapolation across human and environmental toxicology, species, endpoints and time scales.
- The methodology of Pillar 2 covers chemical and biological read-across (**chemical-chemical and species-species extrapolation**), in vitro testing, optimization of in vivo protocols and **mechanism-targeted genomics**, and in silico techniques.

Pillar 3: Exposure

- Objective: To develop criteria for exposure informed testing as foreseen in the REACH regulation, and to **refine relevant exposure assessment methods** accordingly.
- The methodology of Pillar 3 covers exposure-based waiving and triggering of experimental testing. Exposures considered are direct human exposure at the workplace and as consumer and environmental exposure of humans and wildlife, and take into account relevant exposure scenarios including use patterns and conditions of use.

Pillar 4: Integration Strategies and Tools

- Objective: To develop weight-of-evidence approaches for ITS based on a computerized decision theory framework ready for web access, optimizing the use of existing data and non-test information, and minimizing the need for new testing in risk assessment procedures.
- The methodology of Pillar 4 addresses all existing and possibly new ITS components. A major challenge is the identification, reduction and management of uncertainty associated with data, models, decision making and lack of knowledge. Technical information is combined with stakeholder views from regulatory authorities and industry to build and disseminate a decision theory framework for ITS, taking into account cost-benefit analyses as well as societal risk perception.

Pillar 5: Case Studies

- Objective: To evaluate the feasibility and effectiveness of the new ITS methodologies and to provide guidance for their use in concrete form, covering major human and environmental endpoints.
- The methodology of Pillar 5 addresses the feasibility and scope of full ITS schemes through comprehensive test applications. It covers human and environmental toxicology, and different exposure routes and chemicals. Cases with complete REACH sets of data provide opportunity for identifying limitations and refinement of ITS. Evaluation of their accuracy, predictivity, savings with respect to animal use, time and costs, and their level of uncertainty as compared to conventional procedures will result in recommendations and guidance for their implementation in REACH.

**Suggestive governmental organization
for priority decision on test substances
under chronic inhalation
carcinogenic toxicity testing approach**

I. 독성시험 관련 정부 조직.기관









국립환경과학원





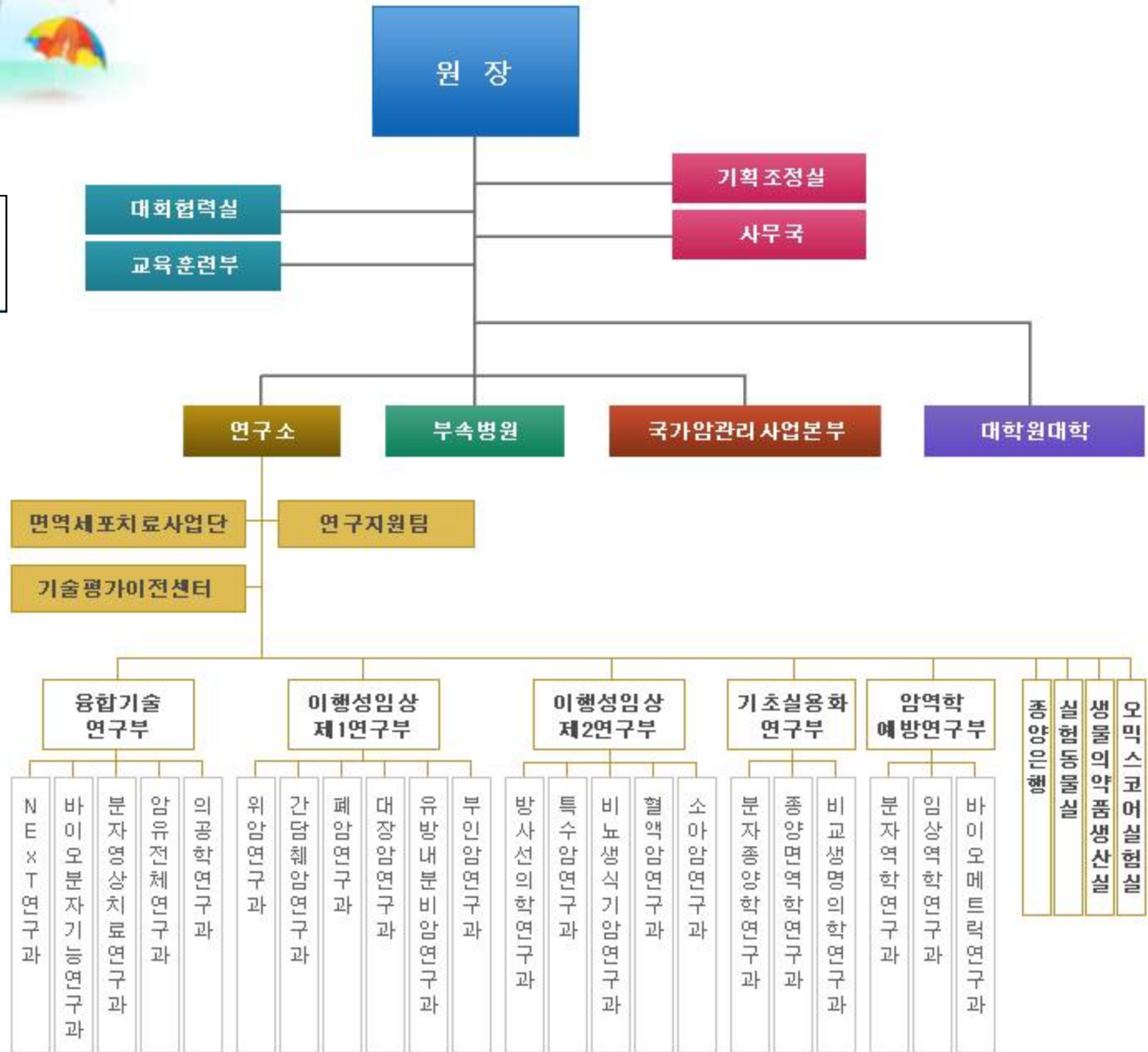
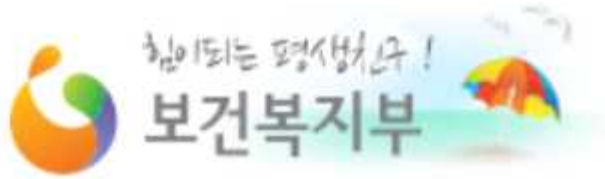
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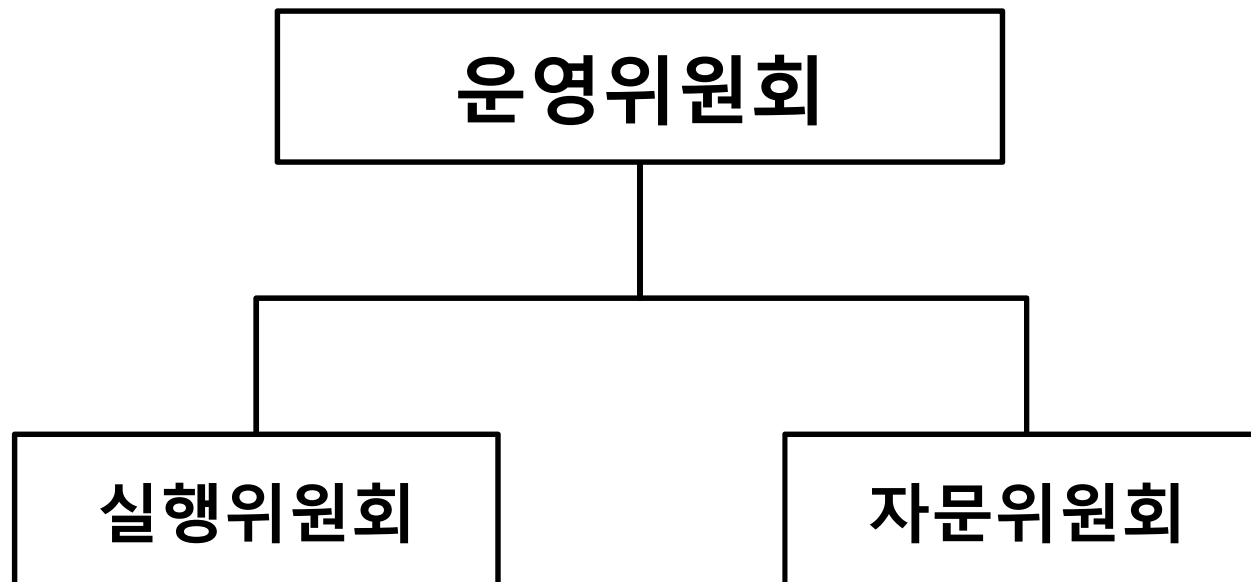
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II. 만성흡입독성/발암성 시험 운영(안)



1. 운영위원회

- 실행위원회 선정 만성흡입성독성 (발암성) 시험 물질 승인
- 실행위원회 제안 물질 시험 계획서 승인
- 시험 결과 보고서 최종 승인
- 시험 결과 국가 정책 반영 협의
- 만성흡입독성 (발암성) 물질 관리 road map 수립
- 시험 소요 비용 등 참여 기관간 현안 해결 등

2. 실행위원회

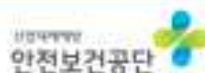
- 만성흡입성독성 (발암성) 시험 물질 추천 :
참여 기관별 매년 1개 시험물질 추천 가능
자문위원회에서도 매년 3개 이하 시험물질 추천 가능
- 추천 시험 물질에 대한 우선 순위 결정을 통한 해당 년도 시험물질 선정
- 선정 시험물질에 대한 시험 계획서 초안 및 최종안 수립 :
초안에 대하여 자문위원회 자문과정을 거친 후 최종안 수립
- 선정 시험물질에 대한 전체 시험 과정 및 결과 검토
- 운영위원회에 시험물질/계획서/결과보고서 승인 요청 등

3. 자문위원회

- 실행위원회 선정 만성흡입성독성 (발암성) 시험 물질에 대한 자문 :
우선 순위에 대한 자문, 시험법 등 시험 계획에 대한 자문
- 시험물질 추천
사회적 현안 관련 시험 물질 추천 등
- 시험 결과 분석 등에 대한 자문
- 운영위원회에 만성흡입독성시험 전반에 대한 자문
- 운영위원회에 만성흡입독성 (발암성) 관리 정책 제안 등

4. 시험기관

한국산업안전보건공단 산업안전보건연구원 화학물질센터
만성흡입독성시험 시설



보도자료

“화학물질 관리 - 위험을 보는 것의 관점의 시작입니다”

- ▶ 보도일시 : 4.30(수) 오전
- ▶ 인터넷 4.30(수) 10.30 이후
- ▶ 총 3쪽(참고자료 1쪽 포함)

▶ 담당 : 화학물질센터 김현영 연구위원
 - TEL : 042-869-0331

‘미확인 독성화학물질 유해성 규명가능’

안전보건공단 국내최초 ‘반성흡입독성 시험시설’ 가공
 저농도·장기간 화학물질 노출 근로자 건강장해 예방 기대

화학물질에 저농도 장기간 노출에 따른 직업성 암이나 인체 유해성을 밝히기 위한 ‘반성흡입독성 시험시설’이 국내 최초로 세워진다.

안전보건공단(이사장 박한기)은 4월 30일 대전광역시 유성구 대덕연구단지에 연면적 6,296㎡에 지상5층 규모의 ‘반성흡입독성 시험시설’ 건립 기공식을 가졌다.

국내에 ‘반성흡입독성 시험시설’이 만들어 지는건 이번이 처음으로, ‘급성흡입독성 시험시설’은 1997년 대덕연구단지에 도입된 바 있다.

이 시설은 과거 알약한 작업환경에서 근로자가 화학물질에 단기간 고농도 노출에 관련된 ‘급성흡입’에 비해, 화학물질에 근로자가 저농도로 장기간 노출에 따른 직업성 암 예방 및 만성독성 예측분야 연구의 필요성으로 만들어 졌다.

이에따라 전자 자동차 타이어 생산공정 등에서 화학물질에 장기간 노출됨에 따라 발생하는 직업병을 연구하게 되며, 관련 알 발생 여부와 나노물질이나 IT산업에서 사용되는 각종 독성 미확인물질에 대한 유해성 평가가 이루어진다.

또한, 시험결과를 바탕으로 화학물질의 유해성 분류와 작업환경 노출기준 설정 등의 유해성 정보를 산업현장에 제공함으로써 근로자 건강보호에 기여할 것으로 기대 된다.

총 370억원의 예산을 들여 2015년 11월에 완공 예정인 이 시설은 48대의 흡입 챔버를 보유하고, 흡입챔버 내에서 실험용 쥐에 화학물질을 노출시켜, 인체에 미치는 유해성을 예측 평가한다.

시험은 실험동물에 화학물질을 2년간 노출하는 만성독성(慢性毒性)시험, 3개월간 노출하는 아만성독성(亞慢性毒性)시험 2시간 이내의 노출인 급성독성(急性毒性)시험이 주로 이루어 진다.

안전보건공단 연구원은 독성시험결과와 국제인증을 통한 신뢰성 확보를 위해 연구윤리 국제표준인 ‘AAALAC’과 연구신뢰성 국제표준인 ‘GLP’ 인증을 추진해 나간다는 방침이다.

* AAALAC(Association for Assessment and Accreditation of Laboratory Animal Care-International) : 실험동물 관리에 관한 국제 평가 및 인증협회

* GLP(Good Laboratory Practice) : 연구인력, 시험시설, 시험방법 등의 우수실험실 기준

한편, 4.30(수)에 열린 기공식에는 박한기 안전보건공단 이사장, 안경덕 고용노동부 산재예방보상정책국장, 조명행 한국독성학회장, 지역 국회의원, 대전광역시 관계자, 노사 및 학계단체 대표자 등 100여명이 참석했다.

안전보건공단 박한기 이사장은 기공식 인사말을 통해 “산업발전과 더불어 국내에는 신규 화학물질의 수와 사용량이 지속적으로 증가하고 있다.”며, “‘반성흡입독성 시험시설’ 건립으로 화학물질의 안전성 확보에 따른 직업성 암 예방과 근로자의 건강장해 예방에 크게 기여할 것으로 기대한다.”고 밝혔다.(끝)

