

# 통합시험평가접근법(IATA)이란?

2020.10.22.

국립환경과학원  
심일섭



# 목 차

- I. 동물대체시험법 필요성 및 동향
- II. OECD IATA 소개
- III. IATA Case Study 현황

# **I. 동물대체시험법 필요성 및 동향**

---

# 미국 Toxic Substances Control Act 개정

- 유해화학물질 관리법(TSCA)은 미국의 화학물질의 안전성을 규제하는 법률로서 1976년 시행됨
- TSCA는 사람과 환경을 보호하기 위해 화학물질의 제조, 가공, 유통을 규제하는 포괄적인 법률
- 40년간 개정이 이루어지지 않았으며, 화학물질 관리에 한계로 인한 개정이 지속적으로 요구됨
- 2009년 TSCA 개혁 6대 원칙을 발표 하였으며, 이를 기초로 2016년 6월 개정됨



United States  
Environmental Protection Agency

EPA Document# EPA-740-R1-8004  
June 22, 2018  
Office of Chemical Safety and  
Pollution Prevention

Strategic Plan to Promote the Development and Implementation of  
Alternative Test Methods Within the TSCA Program

Public Law 114-182  
114th Congress

An Act

To modernize the Toxic Substances Control Act, and for other purposes.

Be it enacted by the Senate and House of Representatives of  
the United States of America in Congress assembled,

SECTION 1. SHORT TITLE; TABLE OF CONTENTS.

(a) SHORT TITLE.—This Act may be cited as the “Frank R.  
Lautenberg Chemical Safety for the 21st Century Act”.

(b) TABLE OF CONTENTS.—The table of contents of this Act  
is as follows:

Sec. 1. Short title; table of contents.

TITLE I—CHEMICAL SAFETY

Sec. 2. Findings, policy, and intent.

Sec. 3. Definitions.

Sec. 4. Testing of chemical substances and mixtures.

Sec. 5. Manufacturing and processing notices.

Sec. 6. Prioritization, risk evaluation, and regulation of chemical substances and  
mixtures.

Sec. 7. Imminent hazards.

Sec. 8. Reporting and retention of information.

Sec. 9. Relationship to other Federal laws.

Sec. 10. Exports of elemental mercury.

Sec. 11. Confidential information.

Sec. 12. Penalties.

Sec. 13. State-Federal relationship.

Sec. 14. Judicial review.

Sec. 15. Citizens' civil actions.

Sec. 16. Studies.

Sec. 17. Administration of the Act.

Sec. 18. State programs.

Sec. 19. Conforming amendments.

Sec. 20. No retroactivity.

Sec. 21. Trevor's Law.

TITLE II—RURAL HEALTHCARE CONNECTIVITY

Sec. 201. Short title.

Sec. 202. Telecommunications services for skilled nursing facilities.

TITLE I—CHEMICAL SAFETY

SEC. 2. FINDINGS, POLICY, AND INTENT.

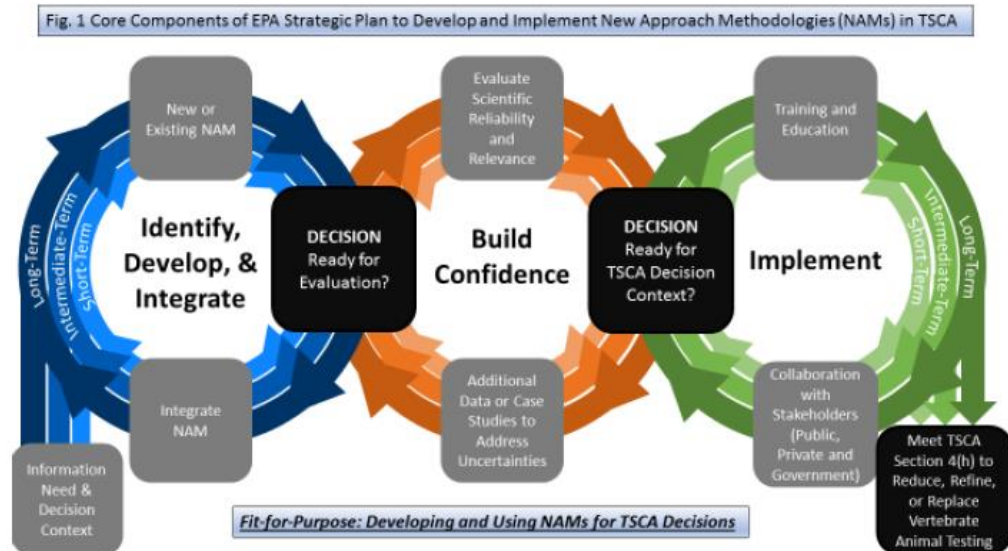
Section 2(c) of the Toxic Substances Control Act (15 U.S.C.  
2601(c)) is amended by striking “proposes to take” and inserting  
“proposes as provided”.

SEC. 3. DEFINITIONS.

Section 3 of the Toxic Substances Control Act (15 U.S.C. 2602)  
is amended—

# US EPA Implementing the Alternative Testing Strategic Plan

- [Strategic Plan](#) published on June 22, 2018
- Core components:
  - 1) Identifying, developing and integrating NAMs for TSCA decisions;
  - 2) Building confidence that the NAMs are scientifically reliable and relevant for TSCA decision s; and
  - 3) Implementing the reliable and relevant NAMs for TSCA decisions



- [Administrator Commitments](#)

*“... The EPA will reduce its requests for, and our funding of, mammal studies by 30 percent by 2025 and eliminate all mammal study requests and funding by 2035.”*

## US EPA New Approach Methods Work Plan (2020.6.)



## Ⅱ. OECD IATA 소개

---

# 주요용어

- Integrated Approach to Testing and Assessment (IATA): 다양한 시험데이터(in vivo, in vitro) 및 비 시험데이터(in silico) 등을 조합하여 유해성을 평가하는 방법론
- Defined Approach (DA): IATA 중 평가에 사용하는 시험데이터의 종류, 판정기준, 평가순서 등을 규정한 방법, DA의 일종으로 ITS 및 STS 가 있음
- Integrated Testing strategy (ITS): DA의 일종으로 다양한 데이터를 동시에 이용하여 평가하는 방법
- Sequential testing Strategy (STS): DA의 일종으로 다양한 데이터를 순차적으로 이용하여 평가하는 방법
- Weight of Evidence (WoE): 몇 개의 독립된 출처에서의 데이터 등을 조합하여 평가하는 방법. 신뢰성이 명확하지 않은 데이터(비GLP시험, QSAR 등)는 여러 데이터간 모순이 없음을 확인한 후, 판단근거로서 사용함
- Grouping: 화학구조가 유사한 화학물질을 그룹화하여 유해성 등을 평가하는 방법
  - category approach와 analogue approach가 있음
- Read-across: 구조적 유사성에 근거하여 데이터 갭을 보완하는 방법. 미시험물질의 유해성은 시험데이터가 있는 유사 물질과 동등하다고 유추함

# Integrated Approach to Testing and Assessment (IATA) 정의

## **What are IATA?**

IATA are pragmatic, science-based approaches for chemical hazard characterisation that rely on an integrated analysis of existing information coupled with the generation of new information using testing strategies.

IATA can include a combination of methods and can be informed by integrating results from one or many methodological approaches [(Q)SAR, read-across, in chemico, in vitro, ex vivo, in vivo] or omic technologies (e.g. toxicogenomics). (OECD, 2020)

Structured approaches used for hazard identification (potential), hazard characterisation (potency) and/or safety assessment (potential/potency and exposure) of a chemical or group of chemicals, which strategically integrate and weight all relevant data and guide the targeted generation of new data where required (hypothesis driven) to inform regulatory decisions regarding potential hazard and/or risk.

IATA is an approach that integrates (and weighs) various sources of information (e.g., physicochemical properties, in silico models, grouping and read-across approaches, in vitro methods, in vivo tests and human data), and newly produced data when required, to inform regulatory decision-making. (D.Krewski et al. 2020)



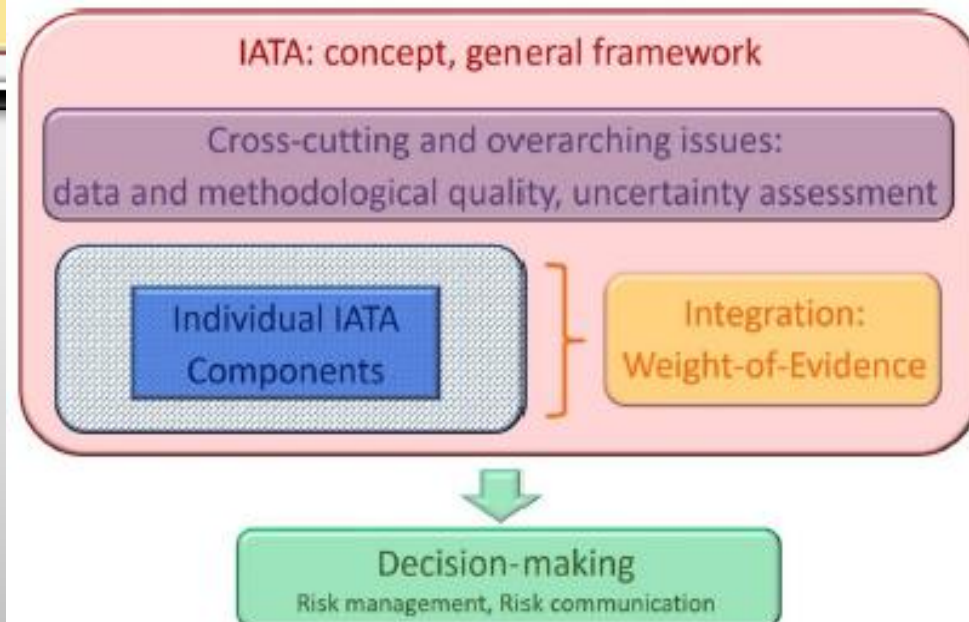
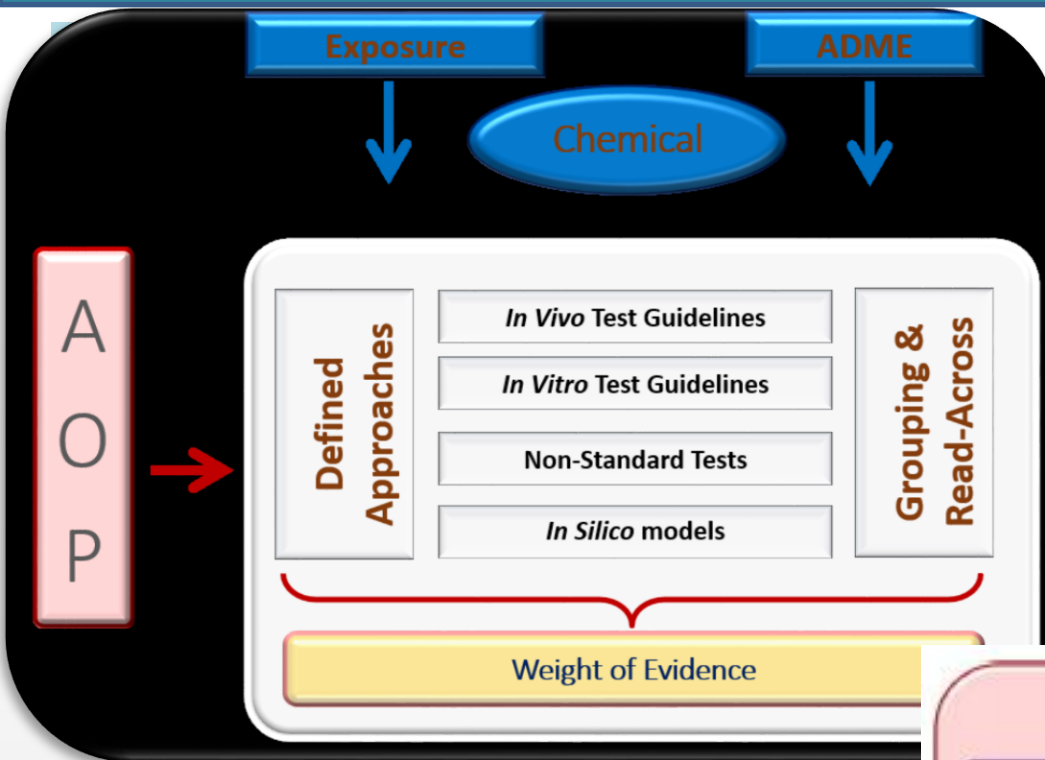
# 시험평가 통합 접근법(IATA)

- IATA (Integrated Approaches to Testing and Assessment)는 화학물질 유해성 또는 위해성 평가를 위한 실용적이고 과학적 접근방법
  - 새로운 정보와 함께 증거력 평가방법(Weight of evidence)을 통해 기존 정보의 통합된 분석방법을 활용
- IATA의 범위는 유연하고 규정화되지 않은 판단 방법(예; Grouping, read-across) 에서부터 규격화되고 명문화된 방법(예, Integrated Testing Strategy(ITS))에까지 해당
- IATA는 다양한 시험(평가) 방법((Q)SAR, read-across, in chemico, in vitro, ex vivo, in vivo)의 적절한 조합으로 이루어질 수 있으며, 여러 종류의 방법 또는 오믹스 기술(예; 독성유전체학)을 통합하여 화학물질 유해성/위해성 결과를 도출함

## IATA (OECD, 2016)

Approach based on multiple information sources used for the hazard identification, hazard characterization, and/or safety assessment of chemicals.

# IATA 구성 요소 및 체계



# DA와 통합시험평가 접근법(IATA)

DAs(Defined Approaches)	IATA (Integrated Approaches to Testing and Assessment)
Structured, Rule-based approaches	Expert judgement-based approaches
e.g. Integrated Testing Strategy (ITS)	e.g. grouping, read-across
Based on a fixed data interpretation procedure(DIP)	ITS+kinetics+exposure+Risk Assessment
prescriptive	Flexible, non-formalized
Generate prediction	Lead to safety conclusions
Validated, harmonized and standardized :Mutual Acceptance of Data	Partially harmonized

# Mutual Acceptance of chemical safety Data

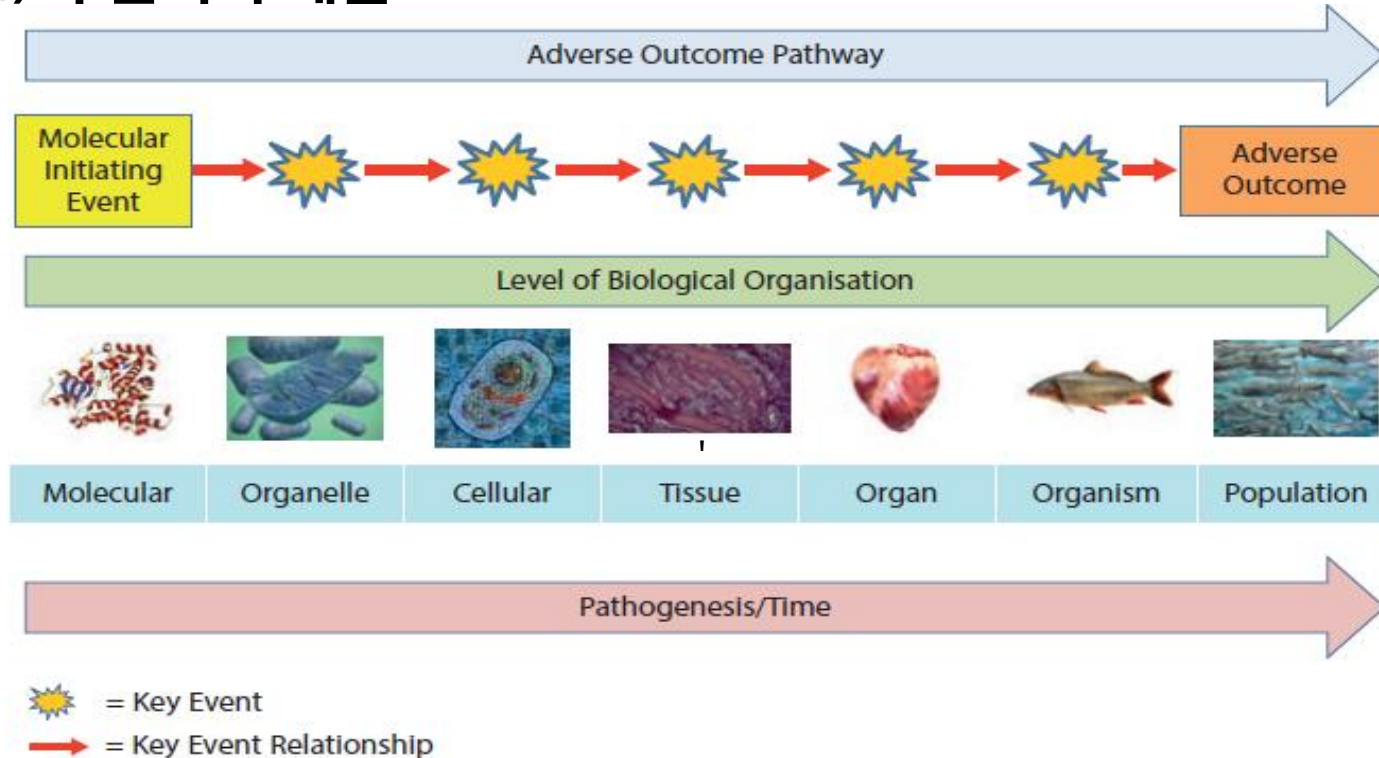


Safety data related to the protection of human health and the environment will be accepted by all 44 countries adhering to MAD

- 37 OECD countries + Argentina, Brazil, India, Malaysia, Singapore, South Africa, Thailand
- Using OECD standards for test methods (Test guidelines)
- Data quality (Principles of Good Laboratory Practice)



**독성발현경로(AOP; Adverse Outcome Pathway)는 여러 생물학적 단계에서 분자수준초기현상(MIE; Molecular Initiating Event)을 독성발현(AO; Adverse Outcome)과 연결하는 주요현상(KE; Key Event)의 논리적 배열**



- KER (Key event relationship)은 상류 KE와 하류 KE사이의 연관 관계를 의미
  - KE 사이의 인과관계를 나타내는 다양한 증거자료를 포함, 정량적 표현 가능
  - 생물학적 과정에서의 상세한 메커니즘 정보를 포함 (biological plausibility)



# OECD IATA 지침문서

- 제목: 시험평가 통합접근법(IATA) 개발을 위한 AOP 활용 지침서

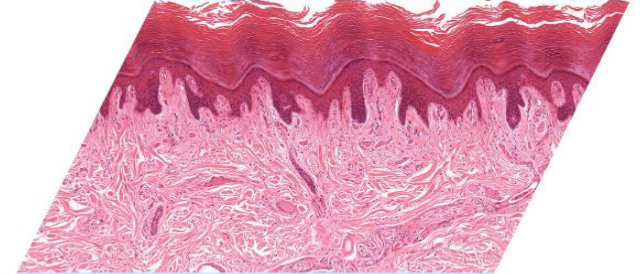
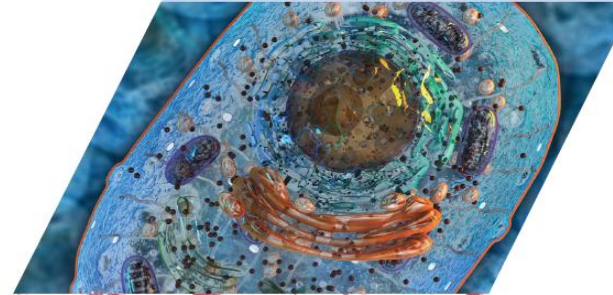
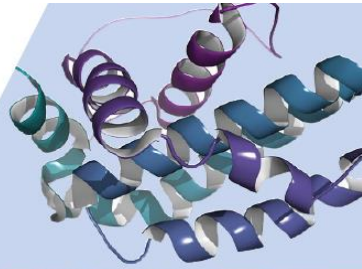
## 발간목적

- IATA 활용과 개발을 위한 체계 제공
- IATA 에 있어서 AOP의 역할 기술
- IATA 개발(QSAR, Grouping, Weight of evidence 등)에 활용되는 AOP 예시 제공

**Guidance Document for the Use of Adverse Outcome Pathways in Developing Integrated Approaches to Testing and Assessment (IATA)**

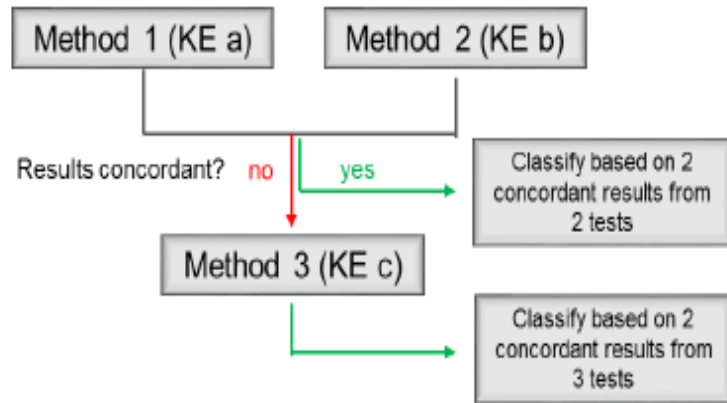


**Series on Testing and Assessment  
No. 260**



# Defined Approach (DA) 예시

Within such IATA there can be one or more DAs, and a greater or lesser degree of expert judgement.

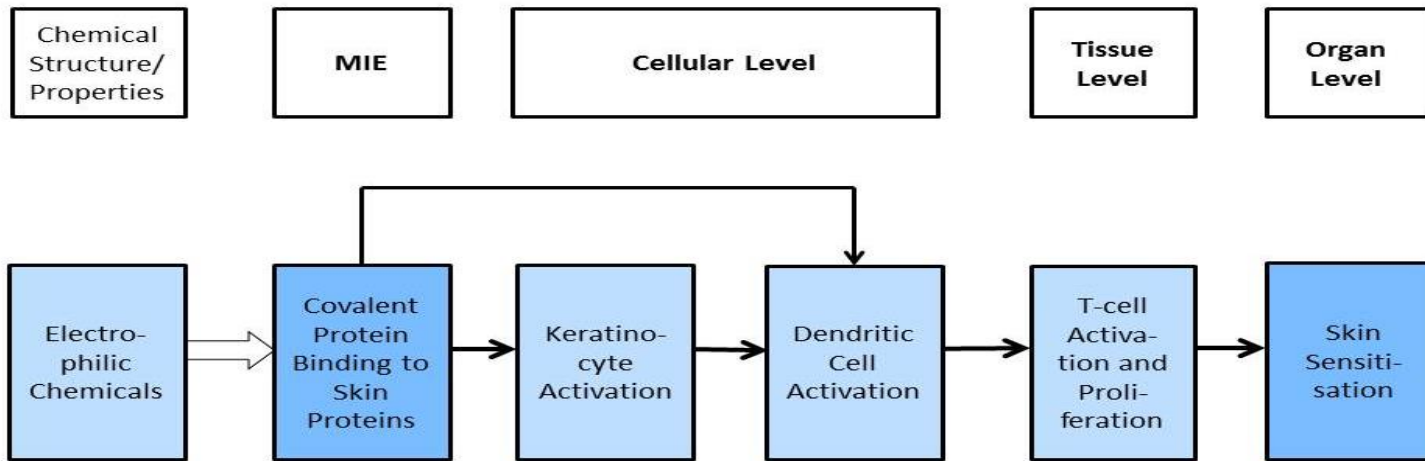


Key event 1 (TG442C): Covalent interaction with cellular proteins  
 DPRA (Direct Peptide Reactivity Assay), or ADRA (Amino acid Derivative Reactivity Assay, 2020추가)

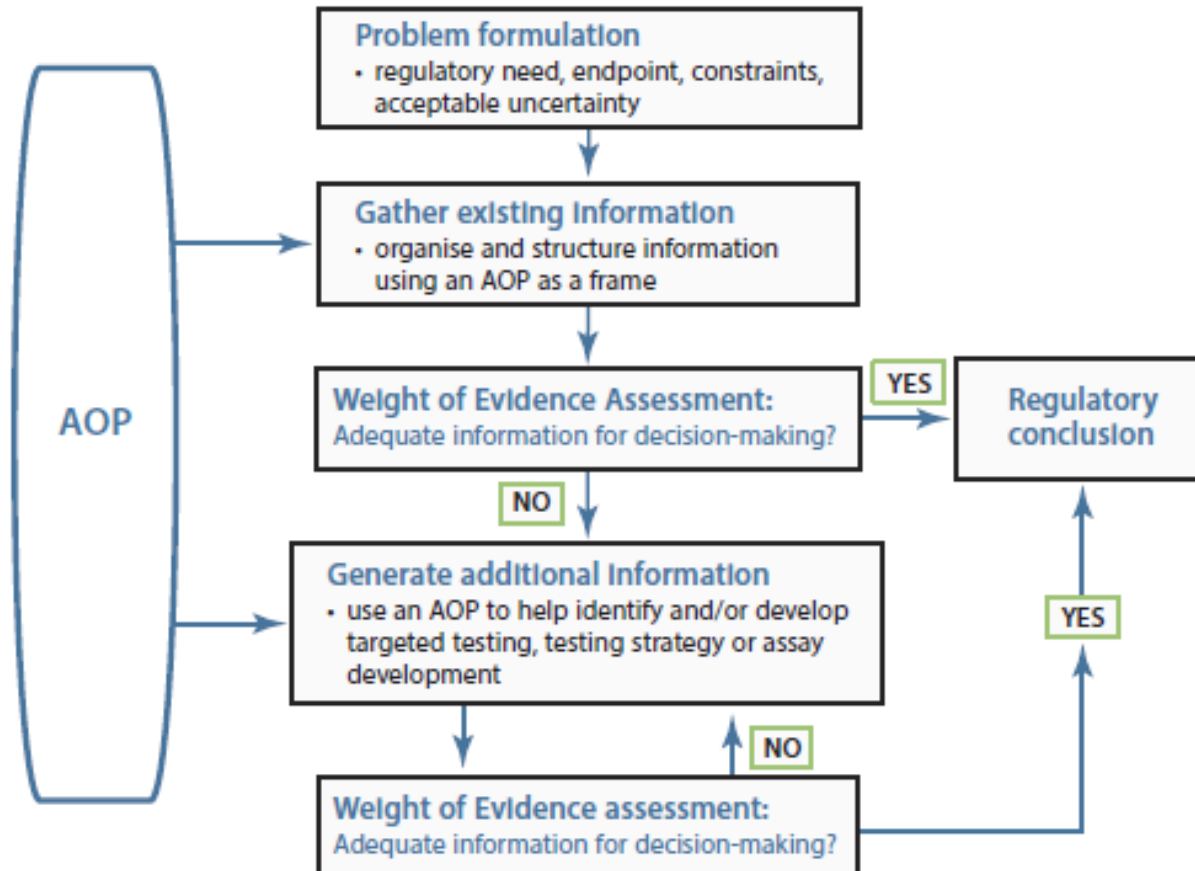
Key event 2 (TG442D): Event in Keratinocytes  
 ARE-Nrf2 Luciferase KeratinoSens or LuSens

Key event 3 (TG442E): Events in Dendritic cell  
 h-CLAT or U-SENS or IL-8

At least two methods predict a substance to be a sensitizer, the substance is considered a skin sensitizer.



# General workflow in Integrated Approaches to Testing and Assessment (IATA)



규제판단을 하는데 요구되는 여러가지 기존 및 추가 정보를 AOP 방법론이 제공 가능



# OECD IATA Guidance Document (GD)

## **No. 203, 2014**

- GD on an IATA for skin corrosion and irritation

## **No. 255, 2016**

- GD on the reporting of DAs to be used with IATA

## **No. 256, 2016**

- GD on the reporting of DAs and individual information sources to be used within IATA for skin sensitisation

## **No. 260, 2016**

- GD for the use of AOP in developing IATA

## **No. 263, 2019(2<sup>nd</sup> Edition)**

- GD on IATA for serious eye damage and eye irritation

- **Guideline Defined Approaches for Skin Sensitisation (DASS),**  
2020년내 승인 예정
  - in vitro와 in silico 방법을 결합한 DA로 in vivo 종말점을 예측
  - 미국, EU, 캐나다 공동 주관

### **III.** IATA Case Study 현황

---

# OECD IATA Case Studies Project

## Objective:

- Increase experience with the use of Integrated Approaches for Testing and Assessment by developing case studies, which constitute examples of predictions that are fit for regulatory use
- Create common understanding of using novel methodologies and the generation of considerations/guidance stemming from these case studies.
- OECD는 2014년 COCAP (Cooperative Chemicals Assessment Programme) 을 개정하여 IATA 개발과 적용을 목표로 하는 활동을 개시하는 IATA Case Studies 프로그램을 발족함
  - 화학물질 유해성 평가를 위한 새로운 방법에 관한 과학적 정보 교환, 기법의 적용방법 및 사례 확립을 목적으로 함
  - 매년 회원국으로부터 제출받은 IATA 를 활용한 평가사례에 관한 문서를 토론하여 평가기법이 규제행정 에 적용가능한지 검토

# OECD IATA Case Studies Project

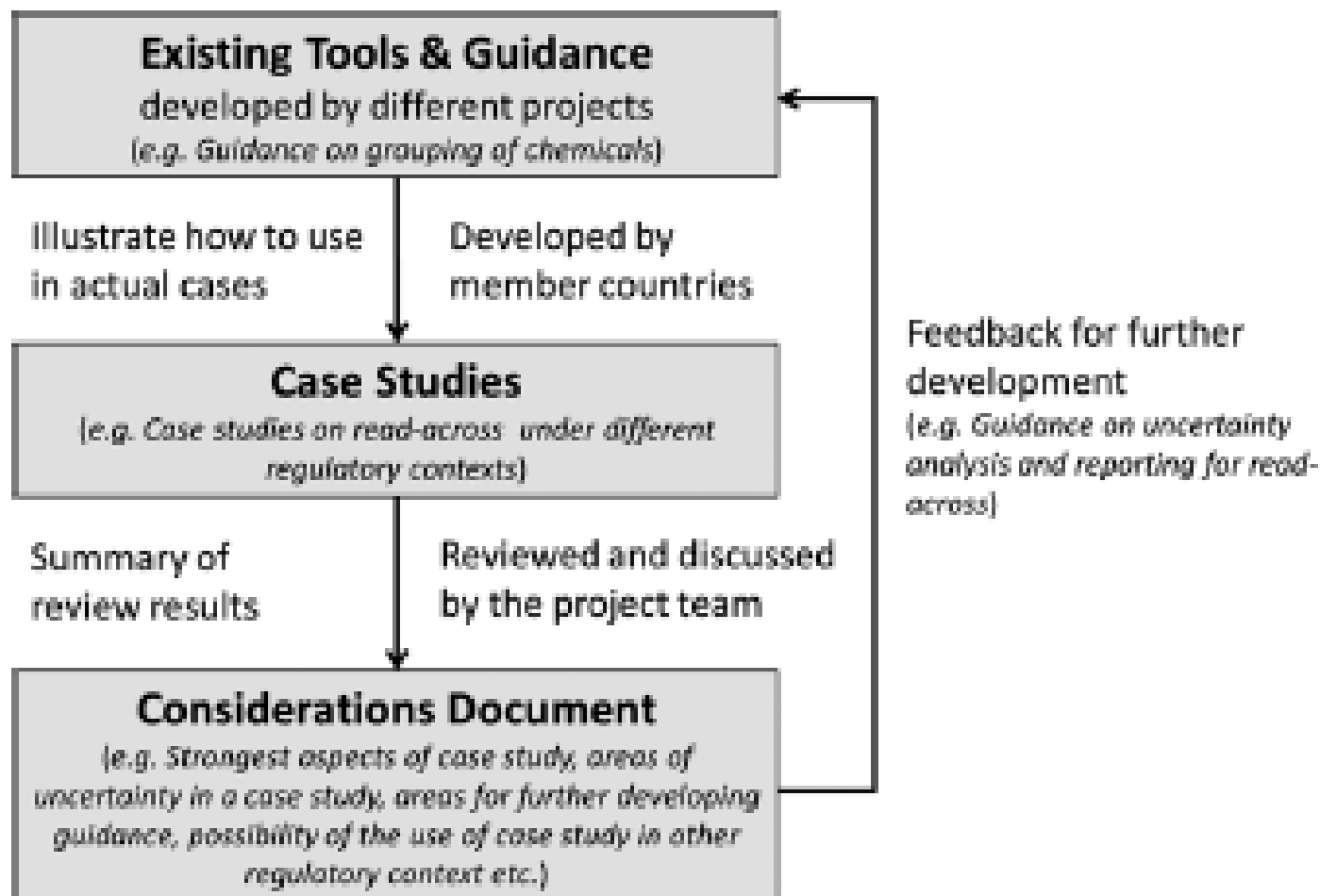


Illustration of the concept of the IATA Case Studies Project (Yuki et al, 2017)

# OECD IATA 사례연구



## ➤ 진행경과: 2019년까지 23건이 검토됨

2015(4건), 2016(5건), 2017(4건): three review cycle of the project

2018: Case studies(2건) reviewed in the fourth review cycle

- Testicular toxicity of ethylene glycol methyl ether(EGME) related chemicals
- Case study on the use of an integrated approach to testing and assessment for estrogen receptor active chemicals

## ➤ 평가 방식

Data gap filling by read-across based on grouping of chemicals(10건)

Grouping of chemicals for cumulative risk assessment, not for read-across(1건)

Safety assessment workflow(1건)

Prioritisation of chemicals (2건)

Defined approach (1건)

## ➤ 검토 주요 항목

- 사례연구의 목적은 분명한가?
- 논리의 정당화는 충분한가? 충분하지 않다면 향상시킬 방법은?
- 사례연구의 장점과 불확실성을 줄이기 위한 방법은?
- 사례연구의 결과를 규제업무에 적용할 수 있는가? 없다면 이유는?
- 검토보고서 형식(template)은 적절한가?

# Summary of the Case Studies Reviewed in the First and Second Review Cycles

Year-No. (Lead)	Assessment approach	Endpoint	IATA topics				References
			AOP*1	UR*2	NAM*3	L/N*4	
2016-1 (Japan)	Read-across	Repeated dose toxicity		X	X		OECD, 2017a
2016-2 (US)	Grouping for cumulative risk assessment	Neurotoxicity	X		X		OECD, 2017b
2016-3 (ICAPO)	Read-across	Repeated dose toxicity		X	X	X	OECD, 2017c
2016-4 (ICAPO)	Read-across	Repeated dose toxicity		X	X	X	OECD, 2017d
2016-5 (JRC/BIAC)	Safety assessment workflow	Repeated dose toxicity	X		X		OECD, 2017e
2015-1 (Canada/US)	Read-across	Mutagenicity	X	X			OECD, 2016b
2015-2 (Canada)	Read-across	Repeated dose toxicity		X	X		OECD, 2016c
2015-3 (Japan)	Read-across	Repeated dose toxicity	X	X			OECD, 2016d
2015-4 (Japan)	Read-across	Bioaccumulation		X		X	OECD, 2016e

\*1: AOP: Use of mode of action/adverse outcome pathways

\*2: UR: Uncertainty reporting

\*3: NAM: Use of new approach methodologies

\*4: L/N: Low/no toxicity prediction

# OECD IATA 사례연구



## ➤ 2019년: 5번째 IATA 검토 과정에서 검토된 8가지 사례 연구 주제

1. Case Study on use of an Integrated Approach to Testing and Assessment (IATA) and New Approach Methods to Inform a Theoretical Read-Across for Dermal Exposure to Propylparaben from Cosmetics [[BIAC \(Cosmetics Europe\)](#)]
2. Case Study on the use of Integrated Approaches for Testing and Assessment for Systemic Toxicity Arising from Cosmetic Exposure to Caffeine [[BIAC \(Cosmetics Europe\)](#)]
3. Case Study on the Use of Integrated Approaches for Testing and Assessment for 90-Day Rat Oral Repeated-Dose Toxicity of Chlorobenzene-Related Chemicals [[BIAC \(Kao\)](#)]
4. Case Study on the Use of Integrated Approaches for Testing and Assessment to Inform Read-across of p-Alkylphenols: Repeated-Dose Toxicity [[BIAC \(Kao\)](#)]
5. Case Study on the use of Integrated Approaches to Testing and Assessment for Prediction of a 90 day Repeated Dose Toxicity Study (OECD 408) for 2-Ethylbutyric Acid Using a Read-Across Approach to Other Branched Carboxylic Acids
6. Case Study on the use of Integrated Approaches to Testing and Assessment for Read-across Based Filling of Developmental and Reproductive Toxicity Data Gap for Methyl Hexanoic Acid [[BIAC \(EU-ToxRisk\)](#)]
7. Case Study on the use of Integrated Approaches to Testing and Assessment for Identification and Characterisation of Parkinsonian Hazard Liability of Deguelin by an AOP-based Testing and Read Across Approach [[BIAC \(EU-ToxRisk\)](#)]
8. Case Study on the use of Integrated Approaches to Testing and Assessment for Mitochondrial Complex-III-Mediated Neurotoxicity of Azoxystrobin? Read-Across to Other Strobilurins [[BIAC \(EU-ToxRisk\)](#)]

# OECD IATA 사례연구



- 2020년: 6번째 IATA 검토 과정에서 검토중인 1가지 사례 연구 주제
  - Case Study on the use of Integrated Approaches for Testing and Assessment for the Systemic Toxicity of Phenoxyethanol when included at 1% in a body lotion [[BIAC \(Cosmetics Europe\)](#)]
- 2021년: 7번째 IATA 검토 과정에서 검토 예정인 2가지 사례 연구 주제(임시)
  - Japan:** Case Study on the Read-Across using PBK model for Haloaliphatic Hydrocarbon Compounds Repeated Dose Toxicity
  - Norway:** Crustacean Endocrine Disrupter (CED) case study



경청해 주셔서 감사합니다

