

Fujifilm announces the adoption of the ADRA, an alternative method for skin sensitization, in the OECD Test Guidelines as a test method for mixtures

Enabling testing on natural extracts used in a wide range of products including cosmetics, detergents and disinfectants

TOKYO, July 27, 2022 – FUJIFILM Corporation (President and CEO, Representative Director: Teiichi Goto) announces that Amino acid Derivative Reactivity Assay (ADRA), an alternative method for skin sensitization, has been adopted in the OECD (Organization of Economic Cooperation and Development) Test Guidelines^{*1} as an internationally reliable test method for mixtures^{*2}. The chemical which can be tested by the ADRA now expanded to mixtures in addition to single chemical^{*3}.

Skin sensitization refers to the skin inflammation or rashes caused as a result of an allergic reaction induced by a chemical when it comes into contact with the skin. Skin sensitization test is carried out prior to product planning or manufacturing process to assess the safety of a chemical. The test is also carried out when the new chemical is developed. Amidst a growing health-conscious trend, many companies are developing products such as cosmetics and detergents that contain natural extracts. A method for testing skin sensitization of mixtures was anticipated. In the process of covalent binding to proteins, which is one of the processes^{*4} for skin sensitization, the ADRA is now the first test method to be adopted in the OECD Test Guidelines.

The ADRA can assess skin sensitization at a high level of accuracy^{*5}, using a reactive reagent with high detection sensitivity developed by Fujifilm in 2017 with the company's advanced chemical synthesis and molecular design capabilities. After the ADRA is adopted in the OECD Test Guidelines for single chemical in 2019, Fujifilm has been promoting the use of the ADRA and undergoing improvement work to expand its scope for skin sensitization test of mixtures.

In the latest development, Fujifilm has made changes to the conventional measuring method of the ADRA to test skin sensitization of mixtures. Specifically, the company has adopted weight concentration^{*6} instead of molar concentration^{*7} as the approach to prepare a test chemical and incorporated the use of fluorescent detector^{*8} in addition to absorbance detector^{*9} depending on test chemical. These changes resulted in achieving skin sensitization test at a high level of accuracy^{*10} for wide variety of mixtures. The revised method underwent a test to validate the reliability of its assessment results and scored 100% in intra- and inter-facility reproducibility test^{*11}. This result was recognized by experts around the world, leading to adoption in the OECD Test Guidelines.

In order to expand the range of use for the ADRA, Fujifilm has been providing the ADRA kit that can easily carry out the ADRA from September 2018 and a contract skin sensitization testing service using the ADRA kit from April 2022 through FUJIFILM Wako Pure Chemical Corporation. Taking advantage of the latest revised method of the ADRA, Fujifilm will proactively propose the use of the ADRA for skin sensitization test of natural extracts, including plant extracts which are widely used in cosmetics, detergents and disinfectants, to the customers such as cosmetics companies, chemical manufacturers and contract testing organizations to expand its range of use.

In its CSR plan "Sustainable Value Plan 2030" setting out targets to be met by FY2030, Fujifilm sets "ensuring product and chemical safety" as one of the priority issues. The company will continue to actively work on developing technologies for ensuring the chemical safety, thereby contributing to minimize the risks for health and environment caused by chemicals.

^{*1} Guidelines published by the OECD for the purpose of ensuring international standardization in test methods for evaluating the characteristics and safety of chemicals.

*2 mixtures and multi-constituent substances.

*3 mono-constituent substances.

*4 There are three processes for skin sensitization: covalent binding to proteins, keratinocyte activation and activation of dendritic cells.

*5 In the validation experiments of a single chemical conducted from October 2016 to April 2017, the ADRA achieved intra-facility reproducibility of 97.3% and inter-facility reproducibility of 91.9%. Yamamoto Y. et al. J Appl Toxicol. 35, 1348-1360 (2015).

*6 One way of indicating the concentration of solution, shown as the weight of a test chemical dissolved in one liter of solvent.

*7 One way of indicating the concentration of solution, shown as the mass of a test chemical dissolved in one liter of solvent.

*8 A device that irradiates light of a specific wavelength and detects a substance that emits light with a wavelength of 220 nm to 900 nm, and measures the fluorescence intensity of that substance.

*9 A device that irradiates ultraviolet rays and detects a substance that absorbs light with a wavelength of 190 nm to 900 nm and measures the absorbance of that substance.

*10 In the validation experiments of a single chemical with the weight concentration conducted from October 2019 to December 2020, the ADRA achieved 100% for both intra-facility reproducibility and inter-facility reproducibility. (Yamamoto Y. et al. J Appl Toxicol. 42, 1078-1090 (2022)).

*11 Intra-facility reproducibility test examines whether test results can be reproduced at the same facility when tests are carried out at different dates or by different testers. Inter-facility reproducibility testing examines whether test results can be reproduced when tests are carried out at multiple different facilities.

About Amino acid Derivative Reactivity Assay (ADRA)

<Conventional measuring method >

- The ADRA is an alternative test for skin sensitization to assess an allergic reaction of skin caused by chemical without using animals. The ADRA reagent possesses a molecular structure of an amino acid derivative with a naphthalene ring which can be detected with high sensitivity using ultraviolet light.
- For assessing skin sensitization of single chemical, the researchers prepare reaction solution that has a fixed molar concentration ratio between the reagent and a chemical being tested, and measuring the amount of reagent that did not combine with the test chemical using the absorbance detector of high-performance liquid chromatography (HPLC). Due to the high-sensitivity detection, the amount of chemical to be tested can be reduced to about one-hundredth of what are required in the conventional "Direct Peptide Reactivity Assay (DPRA)"^{*12}.

<Changes made to conventional measuring method to test skin sensitization of mixtures>

- (1) Change to the weight concentration approach: Natural extracts often have unknown chemicals, causing difficulty in calculating their molar concentration. In response, Fujifilm identified the optimum weight concentration (0.5mg/mL) to prepare solution instead of adopting molar concentration.
- (2) Utilization of a fluorescent detector: There are some cases which an absorbance detector has difficulty in accurately measuring the amount of uncombined reagent. In response, HPLC's fluorescent detector has been utilized, based on the fact that the ADRA reagent contains a naphthalene ring that emits fluorescent light. A fluorescent detector is used in addition to an absorbance detector.

With above two changes, it is possible to measure the amount of the ADRA reagent that did not combine with test chemical.

In order to verify the test results obtained with this assay, Fujifilm carried out reproducibility test from October 2019 to December 2020. Ten types of chemicals were assessed three times each at five facilities to verify whether the results were identical within the same facilities and between different facilities. There was 100% reproducibility.

*12 A method for evaluating skin sensitization by using high-performance liquid chromatography (HPLC) to measure the amount of the peptide remaining unbound to a chemical after the peptide has been added to the chemical.

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