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A Comprehensive Review of the Direct Peptide Reactivity Assay in Skin Sensitization Testing: Applicability, Limitations, and Considerations

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Abstract

Skin sensitization is a crucial endpoint in the safety assessment of chemicals, with the Direct Peptide Reactivity Assay (DPRA) emerging as a valuable *in chemico* method for evaluating a substance's sensitization potential. This review delves into the principles, applicability, and limitations of the DPRA within the context of the Adverse Outcome Pathway (AOP) framework for skin sensitization. We examine the DPRA's role in addressing the molecular initiating event of skin sensitization, its integration into Integrated Approaches to Testing and Assessment (IATA), and its performance in predicting sensitizers. The review also highlights the challenges in testing certain categories of chemicals and the importance of considering the DPRA's results alongside other complementary methods. By providing a comprehensive overview of the DPRA, this review aims to inform researchers, regulators, and clinicians about its utility and limitations in the context of skin sensitization testing.

Key words: DPRA, *in chemico* method, skin sensitization

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Introduction

Direct peptide reactivity assay and adverse outcome pathway

In the realm of pharmaceuticals, the evaluation of dermal sensitization potential is a critical aspect of ensuring the safety of compounds. A skin sensitizer is defined by the United Nations' Globally Harmonized System (GHS) of Classification and Labelling of Chemicals as a substance that can elicit an allergic reaction upon skin contact (1). The mechanistic understanding of skin sensitization is encapsulated in the Adverse Outcome Pathway (AOP) model.

The AOP framework, introduced in 2010 by Ankley et al. (2), is designed to organize and utilize information on the biological and toxicological effects of substances for research and risk assessment. It integrates various types of data across different biological levels to construct a logical, biologically based argument that predicts the consequences of an initiating event. The AOP concept centers around the idea that toxicity starts with an initial interaction between a stressor (e.g., a chemical or virus) and a biomolecule (e.g., a protein or receptor), known as the molecular initiating event (MIE). This event triggers a series of intermediate events (IEs) or key events (KEs), which are linked by key event/effect relationships (KERs) that provide evidence for the causality between them. These events ultimately lead to an adverse outcome (AO), which occurs at the individual level for human health endpoints or at the population level for environmental endpoints (3).

AOPs are not intended to capture all details, but rather the essential KEs and their cause-effect relationships. KEs should be essential for the pathway to progress, meaning each KE is essential for the occurrence of the next one, and hence essential to the outcome. Importantly, KEs must be measurable. Quantitative information in KERs defines how much change in the upstream KE is needed to elicit a detectable change in the downstream KE, in terms of correlations, response-response relationships, dose-dependent transitions, or thresholds of change needed. Thus, a single AOP proposes one biological pathway leading to an AO and a set of methods to measure and predict it.

The Organisation for Economic Co-operation and Development (OECD) has established guidance for AOP development and maintains an online platform called AOP wiki (https://aopwiki.org/), where all AOPs developed (around 300 so far) are openly accessible to interested researchers, regulators, and clinicians (4, 5).

AOPs are widely acknowledged as useful tools in chemical safety assessment and regulatory toxicology for predicting AOs relevant for human and environmental health. The utility of AOPs for regulatory application is defined by the confidence with which AOPs facilitate extrapolation of data measured at low levels of biological organization (molecular and cellular-based methods) to predicted outcomes in organs, individuals, or populations. AOP can also be used for assessing the mechanistic plausibility for epidemiological observations, such as the relationships between the exposure to chemicals or nanomaterials and a risk for a disease. While currently mainly exploited in toxicology, AOPs could also have great value for biological research. Human diseases

are generally classified based on clinical phenotypes. Transition to a mechanistically based understanding of diseases could facilitate the identification of personalized treatment, link mechanistic knowledge to human clinical or epidemiological data, and allow diverse fields to profit from growing networks of the effects of chemical and non-chemical stressors (3, 5, 6).

Skin sensitization is an immunological process that unfolds in two stages: the induction of sensitization and the subsequent triggering of the immune response. The initial stage involves a series of sequential events outlined in AOP40. The MIE is the covalent binding of a substance to skin proteins (specifically, cysteine and/or lysine residues), which leads to the activation of keratinocytes, a key cellular event. Another crucial cellular event is the activation of dendritic cells, triggered by hapten-protein complexes and signals from activated keratinocytes. These dendritic cells then mature and migrate from the epidermis to the local lymph node, where they present parts of the hapten-protein complex to naive T-lymphocytes (T-cells) via major histocompatibility complex molecules. This interaction prompts the differentiation and proliferation of allergen-specific memory T-cells, marking the subsequent key event in the development of sensitization, an AO at the organ level. Once sensitized, an individual can mount a faster secondary response to the same chemical upon re-exposure, either at the same or a different skin site, leading to an aggressive immune response and resulting in allergic contact dermatitis (Figure 1) (7, 8).

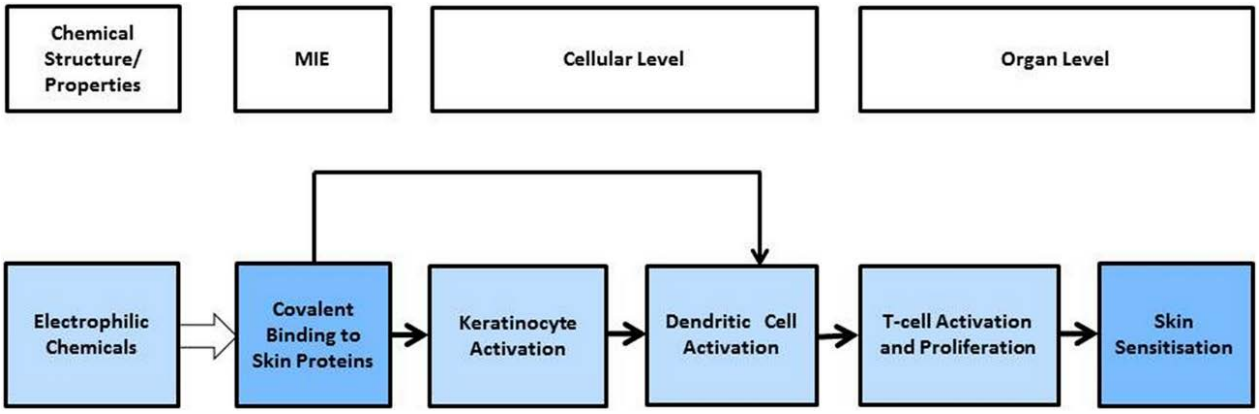

Figure 1. AOP40 (9)
Slika 1. AOP40 (9)

The Direct Peptide Reactivity Assay (DPRA) method is closely linked to AOP40. Specifically, the DPRA addresses the molecular initiating event of AOP40 by quantifying the reactivity of chemicals with synthetic peptides containing cysteine or lysine, providing crucial insights into the potential skin sensitization of a substance.

The aim of this review is to provide a comprehensive overview of the Direct Peptide Reactivity Assay (DPRA) test, including its applicability, limitations, and considerations

for use in skin sensitization testing. We will explore the principles and methodologies underlying the DPRA, evaluate its performance in predicting skin sensitizers, and discuss its role within the broader context of alternative methods and integrated testing strategies.

While there are existing reviews on the DPRA, such as the critical review by Roberts (2021) on the kinetic DPRA (kDPRA), this review provides a distinct perspective by focusing on the broader applicability and limitations of the DPRA within the context of the AOP framework for skin sensitization. Additionally, this review offers an updated and comprehensive synthesis of recent literature, addressing gaps and advancements in the field since the publication of previous reviews (10).

Methodology

Literature Search

To ensure a comprehensive understanding of the Direct Peptide Reactivity Assay (DPRA) within the context of skin sensitization testing, a systematic literature search was conducted. PubMed and Web of Science (WoS) were selected as the primary databases due to their extensive coverage of biomedical and scientific literature, which is highly relevant to our review topic on the Direct Peptide Reactivity Assay (DPRA) and skin sensitization.

The following search strings were employed to capture relevant publications:

PubMed:

((DPRA) OR ("direct peptide reactivity assay")) AND ((chemical) OR (substance*) OR (drug*) OR (compound*)) AND ((assessment*) OR (application*)) AND ((skin) OR (sensitization*))*

WoS:

ALL=(((DPRA) OR ("direct peptide reactivity assay")) AND ((chemical) OR (substance*) OR (drug*) OR (compound*)) AND ((assessment*) OR (application*)) AND ((skin) OR (sensitization*)))*

The search terms were meticulously chosen to ensure the inclusion of all publications relevant to the DPRA's application in assessing skin sensitization. The literature search was conducted on January 6, 2023, with no publication time restriction. The search strings were designed to balance comprehensiveness with specificity to the DPRA's application in skin sensitization. However, to address concerns about potential omissions, a broader search was conducted using the query ((DPRA) OR ("direct peptide reactivity assay")) AND ((skin*) OR (sensitization*)), which yielded 134 records. These additional records were reviewed, and it was determined that the key findings relevant to the scope of this review were captured in the original 79 records. Of the 79 records identified, 45 were from PubMed and 34 from Web of Science. The differences in search results between the two databases were mainly due to their distinct indexing terms and coverage.

Screening Process

The identified records were then imported into Zotero for organization and deduplication. The title and abstract of each record were screened for relevance using the SysRev web platform (www.sysrev.com) by three independent reviewers (EO, EB, and BI) until each record had been screened by at least two reviewers. The criteria for screening titles and abstracts included relevance to the DPRA and skin sensitization, with a focus on applicability and limitations. Conflicts between reviewers were resolved through discussion, ensuring a consensus-based selection of studies for full-text review.

The studies deemed potentially relevant were advanced to the next stage—full-text screening. This was also conducted using SysRev, and the same three reviewers independently assessed each study for eligibility. Fifteen studies (n=15) were ultimately included in the review. The SysRev platform was utilized for its ability to facilitate collaborative screening and data extraction. This web-based tool allowed for a structured and transparent review process, enabling multiple reviewers to work simultaneously and efficiently. The platform's features, such as conflict resolution, enhanced the reliability and consistency of the screening process.

Inclusion Criteria

For a study to be included in the review, it had to meet the following criteria:

- The study must involve the use of the DPRA in the assessment of skin sensitization potential.
- The study must provide data on the application of the DPRA to chemicals, substances, drugs, or compounds.
- The study must be published in English and available in full text for review.

The inclusion criteria were designed to ensure that the studies selected were directly relevant to the DPRA's use in assessing skin sensitization potential, providing a focused and relevant review of the literature.

Results and discussion

Direct peptide reactivity assay and skin sensitisation assessment

Traditionally, the evaluation of skin sensitization has relied heavily on the use of laboratory animals. The Guinea Pig Maximisation Test (GPMT) by Magnusson and Kligman and the Buehler Test (OECD TG 406) (11), which utilize guinea pigs, assess both the induction and elicitation phases of skin sensitization. Mouse-based tests, such as the Local Lymph Node Assay (LLNA) (OECD TG 429) (12) and its non-radioactive variants — LLNA:DA (OECD TG 442A) (13), LLNA:BrdU-ELISA, and BrdUFCM (OECD TG 442B) (14) — focus solely on the induction phase and are favored for their animal welfare benefits and objective assessment of skin sensitization induction. However, the development of *in chemico* and *in vitro* methods based on mechanistic understanding has led to the recognition of alternative approaches for evaluating chemical hazards. Among these, the Direct Peptide Reactivity Assay (DPRA) is notable for its

capacity to address the molecular initiating event in the skin sensitization AOP40 by measuring the reactivity of chemicals with synthetic peptides containing cysteine or lysine. The resulting peptide depletion values help categorize a substance's reactivity and differentiate between sensitizers and non-sensitizers (15, 16). Additionally, OECD TG 442D evaluates keratinocyte activation (17), the second key event, and OECD TG 442E assesses dendritic cell activation (18), the third key event in the skin sensitization AOP. The fourth key event, T-cell proliferation, is indirectly evaluated in the murine Local Lymph Node Assay (LLNA) (12).

The DPRA has undergone validation by the European Union Reference Laboratory for Alternatives to Animal Testing (EURL ECVAM) and has been independently reviewed by the EURL ECVAM Scientific Advisory Committee (ESAC) (19). Table 1 presents a summary of the primary KEs and the current state of testing methods for skin sensitization that are both validated and scientifically accepted.

Table 1. Validated and scientifically accepted test methods for assesssing skin sensitisation potential

Tabela 1. Validirane i naučno prihvaćene metode testiranja za procenu preosetljivosti kože

AOP	**Assay**	**Regulatory Status**	**OECD Test Guidelines**
KE1 Interaction with protein	DPRA	Validated and accepted	TG442C
KE2 Keratinocyte activation	KeratinoSens™	Validated and accepted	TG442D
	LuSens		
KE3 Dendritic cell activation	h-CLAT	Validated and accepted	TG442E
	U-SENS™		
	IL-8 Luc Assay		
	GARD skin		

Direct peptide reactivity assay applicability

As protein reactivity is just one key event in the skin sensitization AOP (8), data obtained from test methods designed to evaluate this specific event may not be adequate on their own to definitively determine whether a chemical has the potential to cause skin sensitization. In a study published in 2019 (20), three different integrated approaches for predicting the risk of human skin sensitization using data from *in vitro* assays, including KeratinoSens™ and the human cell line activation assay (h-CLAT), together with a newly developed chemical assay, the Peptide Direct Reactivity Spectrophotometric Assay (Spectro -DPRA), were evaluated. The study showed that combining the results of *in chemico* and *in vitro* tests improved the prediction compared to individual tests. It is significant to state that the highest predictiveness was achieved by the approach that

included Spectro-DPRA as an initial determinant, followed by the final determination using the results of the KeratinoSens™ and h-CLAT tests (with 96.3% sensitivity, 87.1% specificity , 86.7% positive predictive value, 96.4% negative predictive value and 91.4% accuracy compared to human data) (20). In another study by Ohtake et al. (21), the DPRA test was applied to investigate potential sensitization to isocyanates known to cause occupational allergies. The test was conducted in combination with another *in vitro* test. This study examined nine commonly used isocyanates using an *in vivo* LLNA (The local lymph node) assay performed in mice and guinea pigs with the Integrated Testing Strategy (ITS). ITS is involved in *in silico* predictions via Derek Nexus (DEREK Nexus® is a modeling software that can be used to predict the likely toxicity of any given chemical structure), for chemical assessment using DPRA and *in vitro* testing with the assay human cell line activation (h-CLAT). The results showed that all nine isocyanates were positive in the LLNA, Derek Nexus and DPRA tests, while seven showed positive results in the h-CLAT test. Notably, hexamethylene diisocyanate was h-CLAT negative, while solubility problems prevented the testing of 1,5-diisocyanatonaphthalene. When using the ITS, skin sensitization estimates are consistent with data obtained from the LLNA for all chemicals. However, compared to LLNA results, potency predictions from ITS tended to underestimate (21).

Hence, it is suggested that the data obtained from the DPRA method be utilized within the framework of Integrated Approaches to Testing and Assessment (IATA). This approach combines the DPRA results with additional relevant information from *in vitro* assays that target different key events of the skin sensitization AOP, as well as non-testing methods such as *in silico* modeling and read-across from chemical analogs (22). The application of data from these methods in Defined Approaches (DAs) — standardized approaches in terms of both the sources of information used and the procedures for making predictions — has been documented (22) and is incorporated into an OECD Test Guideline (TG) on defined approaches for skin sensitization (23).

The DPRA is instrumental in distinguishing between skin sensitizers (Category 1) and non-sensitizers. In certain regulatory contexts, positive results from these methods might be sufficient to classify a chemical as a UN GHS Category 1 sensitizer. Nonetheless, these testing methods alone are not capable of further dividing skin sensitizers into subcategories 1A and 1B (24), as defined by the UN GHS (1) for jurisdictions that adopt these two optional subcategories, nor can they predict the potency of a sensitizer for safety assessment purposes (25). For regulatory purposes, the structured or tiered approach utilizing computational, chemical, and laboratory methods is recognized as the principle of Next Generation Risk Assessment (NGRA) and IATA. These concepts were outlined by the Organisation for Economic Co-operation and Development (OECD) (23).

The DPRA test method is characterized by its transferability, reproducibility, and applicability across a broad range of organic functional groups and skin sensitization potencies. The DPRA has demonstrated its ability to be effectively transferred to laboratories that possess expertise in high-performance liquid chromatography (HPLC)

analysis. Within individual laboratories, the consistency of the test method's predictions is approximately 85%, whereas across different laboratories, the reproducibility rate is about 80% (26). According to validation studies (27) and published research (20), the DPRA's capability to differentiate between sensitizers (i.e., UN GHS Category 1) and non-sensitizers has an accuracy rate of 80% (N=157), with a sensitivity of 80% (88/109) and a specificity of 77% (37/48) when compared to the results of the Local Lymph Node Assay (LLNA). It has been observed that the DPRA is more likely to underpredict chemicals with low to moderate skin sensitization potency (i.e., UN GHS subcategory 1B) compared to those with high potency (i.e., UN GHS subcategory 1A) (24, 27) However, the accuracy values provided for the DPRA as an independent test method should be viewed as indicative rather than definitive. It is essential to consider the DPRA results in conjunction with other sources of information within the framework of IATA or DA. Furthermore, it is crucial to acknowledge that non-animal methods for skin sensitization, including the LLNA and other animal tests, may not completely mirror human scenarios, highlighting the importance of a comprehensive and integrated approach to safety assessment (15, 18).

In the paper published by Natsch et al., three *in vitro* tests were validated: the U937 test, the DPRA and the KeratinoSensTM test. Revalidation was tested by comparing the data obtained by applying these tests to 145 chemicals shown to cause skin sensitization in *in vivo* models, after which a database was created. With this study, the authors showed which tests give false positive and false negative results and pointed out the limitations of some tests, including the DPRA test itself (24). In another study, Kolle et al. compared the results of skin sensitization tests obtained by *in vitro* and *in chemico* methods, which were tested on 12 plant extracts and 15 polymer materials, with available *in vivo* data on skin sensitization. Eight plant extracts were tested in a direct peptide reactivity assay (DPRA) and a human cell activation assay (h-CLAT), with a "2 out of 3" approach yielding a balanced accuracy of 50%. For 11 plant extracts evaluated using the Sensitization Information System (SENS-IS), the balanced precision was 88%. Regarding polymeric materials, excluding five polymers with inconclusive *in vitro* results, the remainder, evaluated using the "2 out of 3" approach, achieved a balanced accuracy of 63%. Although these results are based on a limited number of substances, they suggest that certain subgroups of substances may be outside the domain of applicability of the methods used. Therefore, careful analysis is necessary before accepting positive or negative results from the DPRA test and other *in vitro* alternative tests used to assess skin sensitization to various chemicals (28).

The DPRA has proven to be versatile in testing chemicals that encompass a broad spectrum of organic functional groups, reaction mechanisms, skin sensitization potency (as established through *in vivo* studies), and physicochemical properties (15, 18).

It was used to test the degradation products of twenty-four fragrance ingredients. Chemical oxidation with the formation of reactive species that can cause skin sensitization has been confirmed. Four of the twenty-four ingredients showed no reactivity in the DPRA test, coumarin, benzyl salicylate, benzyl cinnamate, and hexyl

cinnamal. The high-throughput with dansyl cysteamine (HTS-DCYA) method, which was used as a comparative test, confirmed the results obtained with the DPRA test. However, compounds cinnamal, cinnamyl alcohol, hydroxycitronellal and lilial were negative in the DCYA but positive in the DPRA method. The results showed that it is necessary to take into account the chemical instability of the tested substances when assessing the skin sensitization potential.

Significant are the results of the DPRA study in which the goal was to evaluate the skin sensitization potential of commercial essential oils of selected *Lamiaceae* species (*Lavandula angustifolia, Melissa officinalis, Mentha longifolia, Thymus vulgaris, Salvia officinalis and Rosmarinus officinalis*) in order to predict their potential allergic properties. DPRA results confirmed that the skin sensitization potential is consistent with data available in the literature on this effect of essential oils. However, some discrepancies were noted when considering the phytochemical properties of the analyzed essential oils and the DPRA results, which further reinforces the need to use a combination of all methods that assess all three key events of the adverse skin sensitization outcome pathway in the assessment of skin sensitization (7)**.**

This extensive applicability highlights the DPRA's effectiveness in detecting skin sensitization hazards across diverse chemical categories. The method's ability to accommodate a wide range of chemical structures and properties enhances its value as a reliable tool in the assessment of skin sensitization potential, contributing to a more comprehensive understanding of chemical safety.

Direct peptide reactivity assay limitations

The DPRA method is not suitable for testing metal compounds, as they are known to react with proteins through non-covalent binding mechanisms. Test chemicals should be soluble in an appropriate solvent at a final concentration of 100 mM, although chemicals not soluble at this concentration can still be tested at lower concentrations. In such cases, a positive result can support the identification of the test chemical as a skin sensitizer, but no definitive conclusion should be drawn from a negative result.

Considering the above, platinum compounds were tested, including hexachloroplatinate and tetrachloroplatinate salts, the strongest known chemical respiratory sensitizers. Eleven platinum compounds were evaluated using DPRA, with minor modifications to the protocol (29). Hexachloroplatinate and tetrachloroplatinate salts showed high reactivity with the cysteine peptide (EC15 values of 1.4 and 14 μM, respectively). However, hydrogen hexahydroxyplatinate and tetraamine platinum for which clinical and epidemiological evidence indicates limited sensitization potential, cysteine DPRA showed little or no reactivity. The results of the lysine peptide tests were less robust, the values being significantly higher than the corresponding results of the cysteine test. This test confirms the value of chemical reactivity of peptides for evaluating platinum sensitization potential. Additional studies are needed to determine whether DPRA can be to some extent potentially applied to other metals (30).

Information on the DPRA's applicability to mixtures of known composition is limited (26, 27), but it is considered technically applicable for testing multi-constituent substances and mixtures of known composition.

Marcelis et al. evaluated the predictive ability of DPRA for individual known substances, but not at the concentrations recommended by the DPRA (100 mM). They used concentrations of LLNA EC3. The applicability of DPRA for testing unknown mixtures of two known skin sensitizers with different potencies, a combination of a skin sensitizer with a non-skin sensitizer, or multiple non-sensitizers, was also evaluated. Experiments revealed that one extremely potent sensitizer (oxazolone) was misclassified as a non-sensitizer when tested at its low EC3 concentration of 0.4 mM instead of the suggested molar excess condition of 100 mM. For binary mixtures, DPRA was able to distinguish all skin sensitizers, and the strongest skin sensitizer in the mixture was decisive for the total reduction of peptides in the test. It was concluded that the DPRA test method can be effectively used for mixtures of known compositions. However, when deviating from the recommended test concentration of 100 mM, one should be careful in case of negative results. Moreover, the test has limitations in application when it comes to mixtures of unknown composition (31).

When testing mixtures, careful consideration should be given to whether the results will be scientifically meaningful. If evidence shows that the test method is not applicable to specific categories of chemicals, it should not be used for those categories.

In the Yamamoto et al. study, the Amino Acid Derivative Reactivity test (ADRA) was developed. ADRA, although based on the same scientific principles as DPRA, shown a much lower frequency of precipitation of the tested chemicals in the reaction solutions than the DPRA test. A comparison of the results for the 82 test chemicals tested by DPRA and ADRA showed that 30 chemicals tested by DPRA showed precipitation in the reaction solution, while only three test substances in the ADRA test showed slight turbidity in the reaction solution. Test chemicals with a n-octanol/water partition coefficient (LogKow) of 2.0 or higher in DPRA show deposition. Only three substances in the ADRA test show turbidity, and all are hydrophobic with a LogKow greater than 6.0. Moreover, one of the test substances in the DPRA assay that caused precipitation gave a false negative result, suggesting that whenever a test chemical shows precipitation in the reaction solution during DPRA testing, the results must be interpreted with great caution, even though not all false positives are caused by the precipitation of the investigated chemicals. (32).

The DPRA test is an *in chemico* method that lacks a metabolic system. Chemicals requiring enzymatic bioactivation to exhibit their skin sensitization potential (i.e., pro-haptens) cannot be detected by this method. Chemicals that become sensitizers after abiotic transformation (i.e., pre-haptens) are generally correctly detected by the test method (26, 33, 34). Therefore, negative results should be interpreted within the context of the method's limitations and in conjunction with other information sources within an IATA or a DA framework. Test chemicals that do not covalently bind to the peptide but

promote its oxidation could lead to an overestimation of peptide depletion, resulting in potential false positive predictions or assignment to a higher reactivity class.

Conclusion

The Direct Peptide Reactivity Assay (DPRA) represents a significant advancement in the *in chemico* assessment of skin sensitization potential, aligning with the principles of the 3Rs (Replacement, Reduction, and Refinement) in animal testing. Its ability to address the molecular initiating event of the skin sensitization AOP provides valuable mechanistic insights into the sensitization process. However, the DPRA is not without limitations, particularly in testing metal compounds, mixtures of unknown composition, and pro-haptens requiring metabolic activation. Therefore, while the DPRA is a critical component of IATA for skin sensitization, it should be used in conjunction with other *in vitro* and *in silico* methods to provide a comprehensive evaluation of a substance's sensitization potential. As the field of toxicology continues to evolve, the DPRA will remain an essential tool in the arsenal of alternative methods for assessing chemical safety.

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NA

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author contributions

Elma Omeragić: Conceptualization, Writing – original draft, Writing - review & editing; **Belma Imamović**: Methodology, Writing - original draft, Writing - review & editing, **Mirza Dedić**: Methodology, Writing - review & editing; **Indira Mujezin**: Methodology, Writing - review & editing; **Ervina Bečić**: Conceptualization, Writing - original draft, Writing - review & editing.

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Sveobuhvatan pregled testa direktne reaktivnosti peptida u ispitivanju preosetljivosti kože: Primenjivost, ograničenja i razmatranja

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Kratak sadržaj

Senzibilizacija kože je ključna tačka u proceni bezbednosti hemikalija, pri čemu se test direktnog reaktiviteta peptida (DPRA) pojavljuje kao dragocena hemijska metoda za procenu potencijala senzibilizacije supstance. Ovaj pregled istražuje principe, primenljivost i ograničenja DPRA u kontekstu okvira nepovoljnog ishoda puta (AOP) za senzibilizaciju kože. Istražujemo ulogu DPRA u adresiranju molekularno inicirajućeg događaja senzibilizacije kože, njegovu integraciju u integrisane pristupe testiranju i proceni (IATA) i njegovu efikasnost u predviđanju senzibilizatora. Pregled takođe ističe izazove u testiranju određenih kategorija hemikalija i važnost razmatranja rezultata DPRA zajedno sa drugim komplementarnim metodama. Pružanjem sveobuhvatnog pregleda DPRA, ovaj pregled ima za cilj da informiše istraživače, regulatorne organe i kliničare o njegovoj korisnosti i ograničenjima u kontekstu testiranja senzibilizacije kože.

Ključne reči: DPRA, hemijska metoda, senzibilizacija kože