

PP4.1. IN SILICO ISPITIVANJA U TOKSIKOLOGIJI: ISKUSTVA, IZAZOVI I PERSPEKTIVE

D. Đukić-Čosić

Univerzitet u Beogradu – Farmaceutski fakultet, Beograd, Srbija

Ispitivanja na životinjama i dalje predstavljaju standard u proceni bezbednosti lekova i hemikalija; međutim, računarski potpomognute (*in silico*) metode se sve više razvijaju kao efikasne alternative ili dopuna *in vivo* ispitivanjima, uz podršku regulatornih okvira kao što je REACH. Njihove prednosti uključuju niske troškove, mogućnost analize hipotetičkih jedinjenja i oslanjanje na podatke relevantne za čoveka, čime se smanjuje ekstrapolacija rezultata između različitih bioloških vrsta. Od sredine 1990-ih, ove tehnologije postaju ključne u razvoju lekova, naročito u proceni ADMET svojstava i predviđanju toksičnih efekata, koji čine značajan deo neuspeha u kasnim fazama razvoja farmaceutika. Bioinformatika i *in silico* pristupi u toksikologiji omogućavaju bržu, etički prihvatljiviju i ekonomičniju procenu bezbednosti hemikalija, u skladu sa 3R principima. Dosadašnja iskustva obuhvataju QSAR modelovanje, identifikaciju toksofora, toksikogenomske analize i rudarenje podataka iz javnih baza. Posebno se izdvajaju rezultati srpsko-kineske saradnje u istraživanju bioaktivnih jedinjenja, gde je *in silico* toksikogenomska analiza sulforafana kod kolorektalnog karcinoma identifikovala genske potpise i molekularne obrasce povezane sa terapijskim efektima, kao i potencijalne neželjene ishode u zavisnosti od genetskog profila pacijenata. Primena koncepta puteva neželjenih ishoda (AOP) i prediktivnih alata dodatno je unapredila razumevanje mehanizama toksičnosti. Uprkos ovim prednostima, izazovi uključuju ograničenu interpretabilnost kompleksnih modela, zavisnost od kvaliteta podataka, nedovoljno precizno modelovanje odnosa doza–odgovor i potrebu za eksperimentalnom validacijom rezultata. Budući pravci razvoja toksikologije zasnivaju se na integrisanim pristupima testiranju i proceni (IATA), koji kombinuju *in silico*, *in vitro* i *in vivo* metode u cilju razvoja pouzdanijih i personalizovanih strategija procene rizika.

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PP4.1. IN SILICO STUDIES IN TOXICOLOGY: EXPERIENCES, CHALLENGES, AND PERSPECTIVES

D. Đukić-Čosić

University of Belgrade – Faculty of Pharmacy, Belgrade, Serbia

Animal testing remains the standard for assessing the safety of drugs and chemicals; however, computer-aided (*in silico*) methods are increasingly being developed as efficient alternatives or complements to *in vivo* testing, supported by regulatory frameworks such as REACH. Their advantages include low cost, the ability to analyze hypothetical compounds, and reliance on human-relevant data, thereby reducing extrapolation of results between different biological species. Since the mid-1990s, these technologies have become essential in drug development, particularly for assessing ADMET properties and predicting toxic effects, which account for a significant proportion of late-stage failures in pharmaceutical development. Bioinformatics and *in silico* approaches in toxicology enable faster, more ethical, and more cost-effective chemical safety assessment, in line with the 3R principles. Previous experience includes QSAR modeling, identification of toxicophores, toxicogenomic analyses, and data mining of public databases. Notably, Serbian–Chinese collaborative research on bioactive compounds demonstrated that *in silico* toxicogenomic analysis of sulforaphane in colorectal cancer identified gene signatures and molecular patterns associated with therapeutic effects, as well as potential adverse outcomes depending on the patient's genetic profile. The application of the Adverse Outcome Pathways (AOP) framework and predictive tools has further improved understanding of toxicity mechanisms. Despite these advantages, challenges remain, including limited interpretability of complex models, dependence on data quality, insufficiently precise dose–response modeling, and the need for experimental validation. Future directions in toxicology rely on integrated approaches to testing and assessment (IATA), combining *in silico*, *in vitro*, and *in vivo* methods to develop more reliable and personalized risk assessment strategies.

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