in 1999 [214], the OECD recommendation was received by the methodology only in mid-2022 [215]. The Pig-a gene encodes the catalytic subunit of N-acetylglucosamine transferase involved in the early synthesis of glycosylphosphatidylinositol [216, 217], which binds protein markers on the surface of homopoietic cells of humans and laboratory mammals (for example, the product of the CD59 gene) [218]. Of all the genes associated with glycosylphosphatidylinositol, the Pig-a gene only is located on the X chromosome [216]. Accordingly, the phenotype characterized by the absence of glycosylphosphatidylinositol will be informative in terms of the presence of mutations at the level of the coding region of the Pig-a gene. In [219], when studying the genotoxic potential of twenty-four chemicals, it was experimentally proved that the Pig-a mutation detection test system is more sensitive when used as indicator cells of reticulocytes. The Pig-a test system with rat peripheral blood cells, in terms of sensitivity to mutagen detection, was significantly inferior to the reticulocyte system [219]. In order to study chemotherapy and radiation therapy schemes in cancer patients, scientific papers [220, 221] consider the possibility of expanding the Pig-a test system in rodents to Pig-A using human erythrocytes.

Scientific papers [222, 223] highlight the issues of assessing the genotoxicity of environmental factors using a promising new model that uses the method of micronucleus analysis with fertilized chicken eggs and erythrocytes. The main advantages of the method include the ability to assess genotoxic effects at the *in vitro* model level, taking into account the parameters of ADME, which are decisive from the point of view of the bioavailability of the chemical compound and associated with its adsorption, distribution, metabolism, release and toxicity. Thus, in accordance with the basic principles of the "3R" concept [168, 169], it becomes possible to obtain an estimate of the genotoxic potential of a certain environmental factor without the additional use of *in vivo* test systems.

In response to the exponential increase in the amount of genotoxic chemicals produced by humanity, the scientific community is becoming more active in finding new approaches to assessing the genetic safety of environmental factors. A significant paradigm shift in genotoxicity testing was observed after the introduction of modern methods for biological sequencing. The development of modern next-generation sequencing (NGS) technologies, followed by the development of a new technology (ecNGS) that allows correcting errors in obtaining reads of DNA fragments, has demonstrated rather good results in detecting somatic mutations induced by environmental factors that have a rather low frequency of occurrence. The scientific paper [224] highlights the basic principles of duplex consensus sequencing, which allows assessing the mutational potential of xenobiotic effects on the human genetic apparatus. The technique makes it possible to identify sequencing artifacts derived from a library preparation at the amplification stage, by comparing the frequency of occurrence of nucleotides at a certain position of a large number of copies of DNA fragments. Mutations caused by environmental factors, according to the consensus duplex sequencing method, will be present in most amplified DNA fragments [224, 225]. The advantage of this method is obtaining information about the genotoxic potential of xenobiotics with a certain localization of damage at the DNA level and their qualitative characteristics. Next-generation sequencing technology based on the approach that allows identifying misread nucleotides provides detailed characterization of induced damage to genetic material at the single nucleotide level, which provides completely new opportunities for solving the problem of complex assessment of mutagenic effects of environmental factors, taking into account the dose-dependent genetic effect [226, 227].

The classical scheme for assessing the genotoxic potential of environmental factors involves the use of a standard battery of *in vitro* and *in vivo* test systems, which have significant disadvantages in terms of time and cost of experimental studies [130, 228, 229]. Furthermore, according to the basic principles of the "3R" concept, it is necessary to reduce the number of studies *with* laboratory animals. In the context of an increase in the number of chemicals that can exhibit genotoxic properties, scientists pay special attention to *in silico* methods that can act as alternative approaches for genetic assessment of environmental factors. The approval of the scientific guideline "ICH M7 Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk" is a defining event that has stimulated the implementation of modern *in silico* models used for obtaining an objective assessment of the mutagenic activity of environmental factors [3, 87, 105, 230] and toxic effects that can be induced by xenobiotics [231, 232]. Computational Toxicology using Qsar (Quantitative Structure-Activity Relationship) *in silico* predictive models in combination with machine learning algorithms and apparatus of mathematical statistics allow us to obtain information about the mutagenic

potential, even in a situation where there are no experimental data on genotoxicity for a particular chemical compound [38]. The use of QSAR *in silico* models are a promising approach for solving regression and binary classification problems for a set of chemicals with unknown genotoxic and toxic properties. The predictive power of such models is based on a set of molecular descriptors that represent the physicochemical, spatial, structural, and electronic properties of a particular xenobiotic under study [111, 233]. The need for research using QSAR models for Computational Toxicology problems is evident in recently published studies [233–236].

Conclusions

In the context of global industrialisation and urbanisation, there is a significant increase in the number of xenobiotics that can be potential environmental pollutants. For a large number of such chemicals, there is no genotoxic assessment, which creates significant obstacles to the study of complex processes associated with the development of hereditary and oncological diseases. Today, the problem of effective identification and consideration of various factors of genetic and carcinogenic danger needs to be solved. Standard toxicology paradigm for conducting genotoxicity testing using a classical battery of *in vitro* and *in vivo* test systems accepted by the scientific community need to update and expand the list of effective and more productive methods, especially taking into account the "3R" concept, which is guided by principles aimed at reducing, improving and replacing animal models in genotoxicity tests. But despite attempts around the world to reduce the number of tests *in vivo* on animals, unfortunately, to date, *in vitro* test systems do not provide complete information about the genotoxic potential, taking into account the three endpoints of DNA damage.

The problems of modern toxicology can be solved through the integration of sciences which were formed and developed in the end of the 20th century. In this context, achievements in bioinformatics and computer science deserve attention. Taking advantage of modern computational QSAR models of toxicology in combination with machine learning algorithms and highly productive next-generation sequencing technologies can be considered as the main vector of development of modern computational toxicology. When forming a new concept of testing for genotoxicity, it is necessary to pay attention not only to solving the problem of binary clysification for potential genotoxic chemical compounds, but also to take into consideration the dose-dependent effect of xenobiotics on the human hereditary apparatus.

Interests disclosure

The authors declare no conflict of interest prior to disclosure.

References

[1] Lander ES, Linton LM, Birren B, Nusbaum C, Zody MC, Baldwin J, et al. Initial sequencing and analysis of the human genome. Nature. 2001 Feb 15;409(6822):860-921. DOI: 10.1038/35057062

[2] 1000 Genomes Project Consortium; Abecasis GR, Altshuler D, Auton A, Brooks LD, Durbin RM, et al. A map of human genome variation from population-scale sequencing. Nature. 2010 Oct 28;467(7319):1061-73. DOI: 10.1038/nature09534

[3] Honma M. An assessment of mutagenicity of chemical substances by (quantitative) structure-activity relationship. Genes Environ. 2020 Jul 2;42:23. doi: 10.1186/s41021-020-00163-1

[4] Engström W, Darbre P, Eriksson S, Gulliver L, Hultman T, Karamouzis MV, et al. The potential for chemical mixtures from the environment to enable the cancer hallmark of sustained proliferative signalling. Carcinogenesis. 2015 Jun;36 Suppl 1(Suppl 1):S38-60. DOI: 10.1093/carcin/bgv030

[5] Sun C, Wei X, Fei Y, Su L, Zhao X, Chen G, et al. Mobile phone signal exposure triggers a hormesis-like effect in Atm+/+ and Atm-/- mouse embryonic fibroblasts. Sci Rep. 2016 Nov 18;6:37423. DOI: 10.1038/srep37423

[6] Tubbs A, Nussenzweig A. Endogenous DNA damage as a source of genomic instability in cancer. Cell. 2017 Feb 9;168(4):644-56. DOI: 10.1016/j.cell.2017.01.002

[7] Valles GJ, Bezsonova I, Woodgate R, Ashton NW. USP7 is a master regulator of genome stability. Front Cell Dev Biol. 2020 Aug 5;8:717. DOI: 10.3389/fcell.2020.00717

[8] Kunkel TA. Celebrating DNA's repair crew. Cell. 2015;163:1301-3. DOI: 10.1016/j.cell.2015.11.028

[9] Martin LJ. DNA damage and repair: relevance to mechanisms of neurodegeneration. J Neuropathol Exp Neurol. 2008 May;67(5):377-87. DOI: 10.1097/NEN.0b013e31816ff780

[10] Lindahl T. Instability and decay of the primary structure of DNA. Nature. 1993;362(6422):709-15. DOI: 10.1038/362709a0

[11] Lindahl T, Barnes DE. Repair of endogenous DNA damage. Cold Spring Harb Symp Quant Biol. 2000;65:127-33. DOI: 10.1101/sqb.2000.65.127
[12] Chen J, Miller BF, Furano AV. Repair of naturally occurring mismatches can induce mutations in flanking DNA. Elife. 2014 Apr 29;3:e02001. DOI: 10.7554/eLife.02001
[13] Nagarathna PKM, Wesley MJ, Reddy PS, Reena K. Review on genotoxicity, its molecular mechanisms and prevention. Int J Pharm Sci Rev Res. 2013;22(1):236-43.
[14] Clarke TL, Mostoslavsky R. DNA repair as a shared hallmark in cancer and ageing. Mol Oncol. 2022 Sep;16(18):3352-79. DOI: 10.1002/1878-0261.13285
[15] Burgess JT, Rose M, Boucher D, Plowman J, Molloy C, Fisher M, et al. The therapeutic potential of DNA damage repair pathways and genomic stability in lung cancer. Front Oncol. 2020 Jul 28;10:1256. DOI: 10.3389/fonc.2020.01256
[16] Chatterjee N, Walker GC. Mechanisms of DNA damage, repair, and mutagenesis. Environ Mol Mutagen. 2017 Jun;58(5):235-63. DOI: 10.1002/em.22087
[17] Milanese C, Cerri S, Ulusoy A, Gornati SV, Plat A, Gabriels S, et al. Activation of the DNA damage response in vivo in synucleinopathy models of Parkinson's disease. Cell Death Dis. 2018 Jul 26;9(8):818. DOI: 10.1038/s41419-018-0848-7
[18] Waller R, Murphy M, Garwood CJ, Jennings L, Heath PR, Chambers A, Met al. Metallothionein-I/II expression associates with the astrocyte DNA damage response and not Alzheimer-type pathology in the aging brain. Glia. 2018 Nov;66(11):2316-23. DOI: 10.1002/glia.23465
[19] Wang H, Li S, Oaks J, Ren J, Li L, Wu X. The concerted roles of FANCM and Rad52 in the protection of common fragile sites. Nat Commun. 2018 Jul 18;9(1):2791. DOI: 10.1038/s41467-018-05066-y
[20] Vaupel J. Biodemography of human ageing. Nature. 2010 Mar 25;464(7288):536-42. DOI: 10.1038/nature08984
[21] Petr MA, Tulika T, Carmona-Marin LM, Scheibye-Knudsen M. Protecting the aging genome. Trends Cell Biol. 2020 Feb;30(2):117-32. DOI: 10.1016/j.tcb.2019.12.001
[22] Kim JJ, Lee SY, Miller KM. Preserving genome integrity and function: the DNA damage response and histone modifications. Crit Rev Biochem Mol Biol. 2019 Jun;54(3):208-41. DOI: 10.1080/10409238.2019.1620676
[23] Horvath S, Raj K. DNA methylation-based biomarkers and the epigenetic clock theory of ageing. Nat Rev Genet. 2018 Jun;19(6):371-84. DOI: 10.1038/s41576-018-0004-3
[24] Wang H, Liu B, Chen H, Xu P, Xue H, Yuan J. Dynamic changes of DNA methylation induced by benzo(a)pyrene in cancer. Genes Environ. 2023 Jul 1;45(1):21. DOI: 10.1186/s41021-023-00278-1
[25] Yasunaga JI, Matsuoka M. Oncogenic spiral by infectious pathogens: Cooperation of multiple factors in cancer development. Cancer Sci. 2018 Jan;109(1):24-32. DOI: 10.1111/cas.13443
[26] Williams VM, Filippova M, Soto U, Duerksen-Hughes PJ. HPV-DNA integration and carcinogenesis: putative roles for inflammation and oxidative stress. Future Virol. 2011 Jan 1;6(1):45-57. DOI: 10.2217/fvl.10.73
[27] Chen Y, Williams V, Filippova M, Filippov V, Duerksen-Hughes P. Viral carcinogenesis: factors inducing DNA damage and virus integration. Cancers (Basel). 2014 Oct 22;6(4):2155-86. DOI: 10.3390/cancers6042155
[28] Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011;144(5):646-74. DOI: 10.1016/j.cell.2011.02.013
[29] Basu AK. DNA damage, mutagenesis and cancer. Int J Mol Sci. 2018 Mar 23;19(4):970. DOI: 10.3390/ijms19040970
[30] Filler RB, Roberts SJ, Girardi M. Cutaneous two-stage chemical carcinogenesis. CSH Protoc. 2007 Sep 1;2007:pdb.prot4837. DOI: 10.1101/pdb.prot4837
[31] Aunan JR, Cho WC, Sшreide K. The Biology of aging and cancer: a brief overview of shared and divergent molecular hallmarks. Aging Dis. 2017 Oct 1;8(5):628-42. DOI: 10.14336/AD.2017.0103
[32] Palmer S, Albergante L, Blackburn CC, Newman TJ. Thymic involution and rising disease incidence with age. Proc Natl Acad Sci U S A. 2018 Feb 20;115(8):1883-8. DOI: 10.1073/pnas.1714478115
[33] Yang JH, Hayano M, Griffin PT, Amorim JA, Bonkowski MS, Apostolides JK, et al. Loss of epigenetic information as a cause of mammalian aging. Cell. 2023 Jan 19;186(2):305-26.e27. DOI: 10.1016/j.cell.2022.12.027
[34] Jeggo PA, Pearl LH, Carr AM. DNA repair, genome stability and cancer: a historical perspective. Nat Rev Cancer. 2016 Jan;16(1):35-42. DOI: 10.1038/nrc.2015.4
[35] Ren N, Atyah M, Chen WY, Zhou CH. The various aspects of genetic and epigenetic toxicology: testing methods and clinical applications. J Transl Med. 2017 May 22;15(1):110. DOI: 10.1186/s12967-017-1218-4
[36] Vega L, Viñes F, Neyman KM. Unravelling morphological and topological energy contributions of metal nanoparticles. Nanomaterials (Basel). 2021 Dec 22;12(1):17. DOI: 10.3390/nano12010017
[37] Ritter L, Kacew S, Krewski D. Integrating emerging technologies into chemical safety assessment: Progress since the 2012 report of the expert panel on the integrated testing of pesticides. Int J Risk AssessManag. 2017;20(1-3):46-58. DOI: 10.1504/IJRAM.2017.082559

[38] Amberg A, Beilke L, Bercu J, Bower D, Brigo A, Cross KP, et al. Principles and procedures for implementation of ICH M7 recommended (Q)SAR analyses. Regul Toxicol Pharmacol. 2016 Jun;77:13-24. DOI: 10.1016/j.yrtph.2016.02.004

[39] Owiti NA, Nagel ZD, Engelward BP. Fluorescence sheds light on DNA damage, DNA repair, and mutations. Trends Cancer. 2021 Mar;7(3):240-48. DOI: 10.1016/j.trecan.2020.10.006

[40] Katerji M, Duerksen-Hughes PJ. DNA damage in cancer development: special implications in viral oncogenesis. Am J Cancer Res. 2021 Aug 15;11(8):3956-79.

[41] Hoeijmakers JH. DNA damage, aging, and cancer. N Engl J Med. 2009 Oct 8;361(15):1475-85. DOI: 10.1056/NEJMra0804615

[42] Brieger K, Schiavone S, Miller FJ Jr, Krause KH. Reactive oxygen species: from health to disease. Swiss Med Wkly. 2012 Aug 17;142:w13659. DOI: 10.4414/smw.2012.13659

[43] Srinivas US, Tan BWQ, Vellayappan BA, Jeyasekharan AD. ROS and the DNA damage response in cancer. Redox Biol. 2019 Jul;25:101084. DOI: 10.1016/j.redox.2018.101084

[44] Fu J, Liao L, Balaji KS, Wei C, Kim J, Peng J. Epigenetic modification and a role for the E3 ligase RNF40 in cancer development and metastasis. Oncogene. 2021 Jan;40(3):465-74. DOI: 10.1038/s41388-020-01556-w

[45] Tirman S, Cybulla E, Quinet A, Meroni A, Vindigni A. PRIMPOL ready, set, reprime! Crit Rev Biochem Mol Biol. 2021 Feb;56(1):17-30. DOI: 10.1080/10409238.2020.1841089

[46] Sharma D, Singh A, Pathak M, Kaur L, Kumar V, Roy BG, et al. DNA binding and antiradical potential of ethyl pyruvate: Key to the DNA radioprotection. Chem Biol Interact. 2020 Dec 1;332:109313. DOI: 10.1016/j.cbi.2020.109313

[47] Verhoven BM, Karim AS, Bath NM, Sarabia Fahl CJ, Wilson NA, Redfield RR 3rd, et al. Significant improvement in rat kidney cold storage using UW organ preservation solution supplemented with the immediate-acting PrC-210 free radical scavenger. Transplant Direct. 2020 Jul 15;6(8):e578. DOI: 10.1097/TXD.0000000000001032

[48] Van Houten B, Santa-Gonzalez GA, Camargo M. DNA repair after oxidative stress: current challenges. Curr Opin Toxicol. 2018 Feb;7:9-16. DOI: 10.1016/j.cotox.2017.10.009

[49] Peng W, Shaw BR. Accelerated deamination of cytosine residues in UV-induced cyclobutane pyrimidine dimers leads to CC-->TT transitions. Biochemistry. 1996 Aug 6;35(31):10172-81. DOI: 10.1021/bi960001x

[50] Moyer R, Briley D, Johnsen A, Stewart U, Shaw BR. Echinomycin, a bis-intercalating agent, induces C-->T mutations via cytosine deamination. Mutat Res. 1993 Aug;288(2):291-300. DOI: 10.1016/0027-5107(93)90097-y

[51] Hayatsu H. Discovery of bisulfite-mediated cytosine conversion to uracil, the key reaction for DNA methylation analysis--a personal account. Proc Jpn Acad Ser B Phys Biol Sci. 2008;84(8):321-30. DOI: 10.2183/pjab.84.321

[52] Frankel AD, Duncan BK, Hartman PE. Nitrous acid damage to duplex deoxyribonucleic acid: distinction between deamination of cytosine residues and a novel mutational lesion. J Bacteriol. 1980 Apr;142(1):335-8. DOI: 10.1128/jb.142.1.335-338.1980

[53] Ganai RA, Johansson E. DNA replication-A matter of fidelity. Mol Cell. 2016;62(5):745-55. DOI: 10.1016/j.molcel.2016.05.003

[54] McCulloch SD, Kunkel TA. The fidelity of DNA synthesis by eukaryotic replicative and translesion synthesis polymerases. Cell Res. 2008 Jan;18(1):148-61. DOI: 10.1038/cr.2008.4

[55] Kunkel TA. Evolving views of DNA replication (in)fidelity. Cold Spring Harb Symp Quant Biol. 2009;74:91-101. DOI: 10.1101/sqb.2009.74.027

[56] Kunkel TA. DNA replication fidelity. J Biol Chem. 2004 Apr 23;279(17):16895-8. DOI: 10.1074/jbc.R400006200

[57] Perrone S, Lotti F, Geronzi U, Guidoni E, Longini M, Buonocore G. Oxidative stress in cancer-prone genetic diseases in pediatric age: The role of mitochondrial dysfunction. Oxid Med Cell Longev. 2016;2016:4782426. DOI: 10.1155/2016/4782426

[58] Carusillo A, Mussolino C. DNA damage: From threat to treatment. Cells. 2020 Jul 10;9(7):1665. DOI: 10.3390/cells9071665

[59] Sander M, Cadet J, Casciano DA, Galloway SM, Marnett LJ, Novak RF, et al. Proceedings of a workshop on DNA adducts: biological significance and applications to risk assessment Washington, DC, April 13-14, 2004. Toxicol Appl Pharmacol. 2005 Oct 1;208(1):1-20. DOI: 10.1016/j.taap.2004.12.012

[60] S, O'Brien JW, Reid MJ, Thomas KV, Praetorius A. From molecular descriptors to intrinsic fish toxicity of chemicals: An alternative approach to chemical prioritization. Environ Sci Technol. 2022 Dec 8. DOI: 10.1021/acs.est.2c07353

[61] Huang R, Zhou PK. DNA damage repair: historical perspectives, mechanistic pathways and clinical translation for targeted cancer therapy. Signal Transduct Target Ther. 2021 Jul 9;6(1):254. DOI: 10.1038/s41392-021-00648-7

[62] Pariset E, Malkani S, Cekanaviciute E, Costes SV. Ionizing radiation-induced risks to the central nervous system and countermeasures in cellular and rodent models. Int J Radiat Biol. 2021;97(sup1):S132-50. DOI: 10.1080/09553002.2020.1820598

[63] Desouky O, Ding N, Zhou G. Targeted and non-targeted effects of ionizing radiation. J Radiat Res Appl Sci. 2015;8:247-54. DOI: 10.1016/j.jrras.2015.03.003

[64] Azzam EI, Jay-Gerin JP, Pain D. Ionizing radiation-induced metabolic oxidative stress and prolonged cell injury. Cancer Lett. 2012 Dec 31;327(1-2):48-60. DOI: 10.1016/j.canlet.2011.12.012

[65] Rastogi RP, Richa, Kumar A, Tyagi MB, Sinha RP. Molecular mechanisms of ultraviolet radiation-induced DNA damage and repair. J Nucleic Acids. 2010 Dec 16;2010:592980. DOI: 10.4061/2010/592980

[66] Lee JW, Ratnakumar K, Hung KF, Rokunohe D, Kawasumi M. Deciphering UV-induced DNA damage responses to prevent and treat skin cancer. Photochem Photobiol. 2020 May;96(3):478-99. DOI: 10.1111/php.13245

[67] Wang Z, Walker GW, Muir DCG, Nagatani-Yoshida K. Toward a global understanding of chemical pollution: A first comprehensive analysis of national and regional chemical inventories. Environ Sci Technol. 2020 Mar 3;54(5):2575-84. DOI: 10.1021/acs.est.9b06379

[68] Chrz J, Hošíková B, Svobodová L, Očadlнková D, Kolářová H, Dvořáková M, et al. Comparison of methods used for evaluation of mutagenicity/genotoxicity of model chemicals - parabens. Physiol Res. 2020 Dec 31;69(Suppl 4):S661-79. DOI: 10.33549/physiolres.934615

[69] Chung KT, Kirkovsky L, Kirkovsky A, Purcell WP. Review of mutagenicity of monocyclic aromatic amines: quantitative structure-activity relationships. Mutat Res. 1997 Aug;387(1):1-16. DOI: 10.1016/s1383-5742(97)00019-7

[70] Ohe T, Takeuchi N, Watanabe T, Tada A, Nukaya H, Terao Y, et al. Quantification of two aromatic amine mutagens, PBTA-1 and PBTA-2, in the yodo river system. Environ Health Perspect. 1999 Sep;107(9):701-4. DOI: 10.1289/ehp.99107701

[71] Nagao M, Honda M, Seino Y, Yahagi T, Sugimura T. Mutagenicities of smoke condensates and the charred surface of fish and meat. Cancer Lett. 1977 Mar;2(4-5):221-6. DOI: 10.1016/s0304-3835(77)80025-6

[72] Neumann HG. The role of DNA damage in chemical carcinogenesis of aromatic amines. J Cancer Res Clin Oncol. 1986;112(2):100-6. DOI: 10.1007/BF00404390

[73] Benigni R, Bossa C. Mechanisms of chemical carcinogenicity and mutagenicity: a review with implications for predictive toxicology. Chem Rev. 2011 Apr 13;111(4):2507-36. DOI: 10.1021/cr100222q

[74] Shamovsky I, Ripa L, Börjesson L, Mee C, Nordén B, Hansen P, et al. Explanation for main features of structure-genotoxicity relationships of aromatic amines by theoretical studies of their activation pathways in CYP1A2. J Am Chem Soc. 2011 Oct 12;133(40):16168-85. DOI: 10.1021/ja206427u

[75] Muz M, Dann JP, Jäger F, Brack W, Krauss M. Identification of mutagenic aromatic amines in river samples with industrial wastewater impact. Environ Sci Technol. 2017 Apr 18;51(8):4681-8. DOI: 10.1021/acs.est.7b00426

[76] Chen X, Jia W, Zhu L, Mao L, Zhang Y. Recent advances in heterocyclic aromatic amines: An update on food safety and hazardous control from food processing to dietary intake. Compr Rev Food Sci Food Saf. 2020 Jan;19(1):124-48. DOI: 10.1111/1541-4337.12511

[77] Norinder U, Myatt G, Ahlberg E. Predicting aromatic amine mutagenicity with confidence: A case study using conformal prediction. Biomolecules. 2018 Aug 29;8(3):85. DOI: 10.3390/biom8030085

[78] Kriek E. Fifty years of research on N-acetyl-2-aminofluorene, one of the most versatile compounds in experimental cancer research. J Cancer Res Clin Oncol. 1992;118(7):481-9. DOI: 10.1007/BF01225261

[79] Chiapella C, Radovan RD, Moreno JA, Casares L, Barbé J, Llagostera M. Plant activation of aromatic amines mediated by cytochromes P450 and flavin-containing monooxygenases. Mutat Res. 2000;470(2):155-60. DOI: 10.1016/s1383-5718(00)00098-x

[80] Shibutani S, Suzuki N, Tan X, Johnson F, Grollman AP. Influence of flanking sequence context on the mutagenicity of acetylaminofluorene-derived DNA adducts in mammalian cells. Biochemistry. 2001;40(12):3717-22. DOI: 10.1021/bi0027581

[81] Arora PK. Bacterial degradation of monocyclic aromatic amines. Front Microbiol. 2015;6:820. DOI: 10.3389/fmicb.2015.00820

[82] Fatima M, Saeed M, Aslam M, Lindström RW, Farooq R. Application of novel bacterial consortium for biodegradation of aromatic amine 2-ABS using response surface methodology. J Microbiol Methods. 2020;174:105941. DOI: 10.1016/j.mimet.2020.105941

[83] Ahlberg E, Amberg A, Beilke LD, Bower D, Cross KP, Custer L, et al. Extending (Q)SARs to incorporate proprietary knowledge for regulatory purposes: A case study using aromatic amine mutagenicity. Regul Toxicol Pharmacol. 2016 Jun;77:1-12. DOI: 10.1016/j.yrtph.2016.02.003

[84] Patel M, Kranz M, Munoz-Muriedas J, Harvey JS, Giddings A, Swallow S, et al. A pharma-wide approach to address the genotoxicity prediction of primary aromatic amines. Comput Toxicol. 2018;7:27-35. DOI: 10.1016/j.comtox.2018.06.002

[85] Furukawa A, Ono S, Yamada K, Torimoto N, Asayama M, Muto S. A local QSAR model based on the stability of nitrenium ions to support the ICH M7 expert review on the mutagenicity of primary aromatic amines. Genes Environ. 2022 Mar 21;44(1):10. DOI: 10.1186/s41021-022-00238-1

[86] Mojiri A, Zhou JL, Ohashi A, Ozaki N, Kindaichi T. Comprehensive review of polycyclic aromatic hydrocarbons in water sources, their effects and treatments. Sci Total Environ. 2019 Dec 15;696:133971. DOI: 10.1016/j.scitotenv.2019.133971

[87] Patel AB, Shaikh S, Jain KR, Desai C, Madamwar D. Polycyclic Aromatic hydrocarbons: Sources, toxicity, and remediation approaches. Front Microbiol. 2020 Nov 5;11:562813. DOI: 10.3389/fmicb.2020.562813

[88] Ewa B, Danuta MŠ. Polycyclic aromatic hydrocarbons and PAH-related DNA adducts. J Appl Genet. 2017 Aug;58(3):321-30. DOI: 10.1007/s13353-016-0380-3

[89] Abdel-Shafy HI, Mansour MS. A review on polycyclic aromatic hydrocarbons: source, environmental impact, effect on human health and remediation. Egypt J Pet. 2016;25:107-23. DOI: 10.1016/j.ejpe.2015.03.011

[90] Zheng H, Xing X, Hu T, Zhang Y, Zhang J, Zhu G, Li Y, Qi S. Biomass burning contributed most to the human cancer risk exposed to the soil-bound PAHs from Chengdu Economic Region, western China. Ecotoxicol Environ Saf. 2018;159:63-70. DOI: 10.1016/j.ecoenv.2018.04.065

[91] Ames BN, Profet M, Gold LS. Dietary pesticides (99.99% all natural). Proc Natl Acad Sci U S A. 1990 Oct;87(19):7777-81. DOI: 10.1073/pnas.87.19.7777

[92] Kumar P, Mahato DK, Kamle M, Mohanta TK, Kang SG. Aflatoxins: A global concern for food safety, human health and their management. Front Microbiol. 2017 Jan 17;7:2170. DOI: 10.3389/fmicb.2016.02170

[93] Frisvad JC, Hubka V, Ezekiel CN, Hong SB, Nováková A, Chen AJ, et al. Taxonomy of Aspergillus section Flavi and their production of aflatoxins, ochratoxins and other mycotoxins. Stud Mycol. 2019 Jun;93:1-63. DOI: 10.1016/j.simyco.2018.06.001

[94] Baranyi N, Despot DJ, Palágyi A, Kiss N, Kocsubé S, Szekeres A, et al. Identification of Aspergillus species in Central Europe able to produce G-type aflatoxins. Acta Biol Hung. 2015 Sep;66(3):339-47. DOI: 10.1556/018.66.2015.3.9

[95] Priesterjahn EM, Geisen R, Schmidt-Heydt M. Influence of light and water activity on growth and mycotoxin formation of selected isolates of Aspergillus flavus and Aspergillus parasiticus. Microorganisms. 2020 Dec 15;8(12):2000. DOI: 10.3390/microorganisms8122000

[96] Booth ED, Rawlinson PJ, Maria Fagundes P, Leiner KA. Regulatory requirements for genotoxicity assessment of plant protection product active ingredients, impurities, and metabolites. Environ Mol Mutagen. 2017 Jun;58(5):325-44. DOI: 10.1002/em.22084

[97] Hayashi M. Opinion: regulatory genotoxicity: past, present and future. Genes Environ. 2022 Apr 22;44(1):13. DOI: 10.1186/s41021-022-00242-5

[98] Jayasekara PS, Skanchy SK, Kim MT, Kumaran G, Mugabe BE, Woodard LE, et al. Assessing the impact of expert knowledge on ICH M7 (Q)SAR predictions. Is expert review still needed? Regul Toxicol Pharmacol. 2021 Oct;125:105006. DOI: 10.1016/j.yrtph.2021.105006

[99] Galloway SM. International regulatory requirements for genotoxicity testing for pharmaceuticals used in human medicine, and their impurities and metabolites. Environ Mol Mutagen. 2017 Jun;58(5):296-324. DOI: 10.1002/em.22077

[100] Williams AJ, Tkachenko V, Golotvin S, Kidd R, McCann G. ChemSpider - building a foundation for the semantic web by hosting a crowd sourced databasing platform for chemistry. J Cheminform. 2010;2(Suppl 1):O16. DOI: 10.1186/1758-2946-2-S1-O16

[101] Kim S, Chen J, Cheng T, Gindulyte A, He J, He S, et al. PubChem 2019 update: improved access to chemical data. Nucleic Acids Res. 2019 Jan 8;47(D1):D1102-D1109. DOI: 10.1093/nar/gky1033

[102] Gabrielson SW. SciFinder. J Med Libr Assoc. 2018 Oct;106(4):588-90. DOI: 10.5195/jmla.2018.515

[103] Buick JK, Williams A, Meier MJ, Swartz CD, Recio L, Gagné R, et al. A modern genotoxicity testing paradigm: Integration of the high-throughput CometChip® and the TGx-DDI transcriptomic biomarker in human HepaRG™ cell cultures. Front Public Health. 2021 Aug 18;9:694834. DOI: 10.3389/fpubh.2021.694834

[104] Araújo R, Ramalhete L, Paz H, Ladeira C, Calado CRC. A new method to predict genotoxic effects based on serum molecular profile. Spectrochim Acta A Mol Biomol Spectrosc. 2021 Jul 5;255:119680. DOI: 10.1016/j.saa.2021.119680

[105] Cronin MTD, Belfield SJ, Briggs KA, Enoch SJ, Firman JW, Frericks M, et al. Making in silico predictive models for toxicology FAIR. Regul Toxicol Pharmacol. 2023 May;140:105385. DOI: 10.1016/j.yrtph.2023.105385

[106] Fortin AV, Long AS, Williams A, Meier MJ, Cox J, Pinsonnault C, et al. Application of a new approach methodology (NAM)-based strategy for genotoxicity assessment of data-poor compounds. Front Toxicol. 2023 Jan 23;5:1098432. DOI: 10.3389/ftox.2023.1098432

[107] Organisation for Economic Co-operation and Development (OECD). Overview on genetic toxicology TGs. In: OECD Series on Testing and Assessment. Paris: OECD Publishing; 2017. DOI: 10.1787/9789264274761-en

[108] Joint meeting of the chemicals committee and the working party on chemicals, pesticides and biotechnology. Overview of the set of OECD Genetic Toxicology. Test Guidelines and updates performed in 2014-2015. Brussels: OECD; 2017.

[109] Mišík M, Nersesyan A, Ferk F, Holzmann K, Krupitza G, Herrera Morales D, et al. Search for the optimal genotoxicity assay for routine testing of chemicals: Sensitivity and specificity of conventional and new test systems. Mutat Res Genet Toxicol Environ Mutagen. 2022 Sep;881:503524. DOI: 10.1016/j.mrgentox.2022.503524

[110] Turkez H, Arslan ME, Ozdemir O. Genotoxicity testing: progress and prospects for the next decade. Expert Opin Drug Metab Toxicol. 2017;13:1089-98. DOI: 10.1080/17425255.2017.1375097

[111] Luan Y, Honma, M. Genotoxicity testing and recent advances. Genome Instab Dis. 2022;3:1-21. DOI: 10.1007/s42764-021-00058-7

[112] Mohamed S, Sabita U, Rajendra S, Raman D. Genotoxicity: mechanisms, testing guidelines and methods. Glob J Pharm Sci. 2017;1(5):555575. DOI: 10.19080/GJPPS.2017.01.555575

[113] Sofuni T. Evolution of genotoxicity test methods in Japan. Genes Environ. 2017 Feb 21;39:15. DOI: 10.1186/s41021-016-0063-7

[114] EFSA Scientific Committee. Scientific opinion on genotoxicity testing strategies applicable to food and feed safety assessment. EFSA J. 2011;9(9):2379. DOI: 10.2903/j.efsa.2011.2379

[115] Organisation for Economic Co-operation and Development (OECD). Test No. 471: Bacterial Reverse Mutation Test. In: OECD Guidelines for the Testing of Chemicals, Section 4. Paris: OECD Publishing; 2016. DOI: 10.1787/9789264071247-en
[116] Organisation for Economic Co-operation and Development (OECD). Test No. 473: In Vitro Mammalian Chromosomal Aberration Test. In: OECD Guidelines for the Testing of Chemicals, Section 4. Paris: OECD Publishing; 2016. DOI: 10.1787/9789264264649-en
[117] Organisation for Economic Co-operation and Development (OECD). Test No. 474: Mammalian Erythrocyte Micronucleus Test. In: OECD Guidelines for the Testing of Chemicals, Section 4. Paris: OECD Publishing; 2016. DOI: 10.1787/9789264264762-en
[118] Organisation for Economic Co-operation and Development (OECD). Test No. 475: Mammalian Bone Marrow Chromosomal Aberration Test. In: OECD Guidelines for the Testing of Chemicals, Section 4. Paris: OECD Publishing; 2016. DOI: 10.1787/9789264264786-en
[119] Organisation for Economic Co-operation and Development (OECD). Test No. 476: In Vitro Mammalian Cell Gene Mutation Tests using the Hprt and xprt genes. In: OECD Guidelines for the Testing of Chemicals, Section 4. Paris: OECD Publishing; 2016. DOI: 10.1787/9789264264809-en
[120] Organisation for Economic Co-operation and Development (OECD). Test No. 478: Rodent Dominant Lethal Test. In: OECD Guidelines for the Testing of Chemicals, Section 4. Paris: OECD Publishing; 2016. DOI: 10.1787/9789264264823-en
[121] Organisation for Economic Co-operation and Development (OECD). Test No. 483: Mammalian Spermatogonial Chromosomal Aberration Test. In: OECD Guidelines for the Testing of Chemicals, Section 4. Paris: OECD Publishing; 2016. DOI: 10.1787/9789264264847-en
[122] Organisation for Economic Co-operation and Development (OECD). Test No. 485: Genetic toxicology, Mouse Heritable Translocation Assay. In: OECD Guidelines for the Testing of Chemicals, Section 4. Paris: OECD Publishing; 2016. DOI: 10.1787/9789264071506-en
[123] Organisation for Economic Co-operation and Development (OECD). Test No. 486: Unscheduled DNA Synthesis (UDS) Test with Mammalian Liver Cells in vivo. In: OECD Guidelines for the Testing of Chemicals, Section 4. Paris: OECD Publishing; 2016. DOI: 10.1787/9789264071520-en
[124] Organisation for Economic Co-operation and Development (OECD). Test No. 487: In Vitro Mammalian Cell Micronucleus Test. In: OECD Guidelines for the Testing of Chemicals, Section 4. Paris: OECD Publishing; 2016. DOI: 10.1787/9789264264861-en
[125] Organisation for Economic Co-operation and Development (OECD). Test No. 489: In Vivo Mammalian Alkaline Comet Assay. In: OECD Guidelines for the Testing of Chemicals, Section 4. Paris: OECD Publishing; 2016. DOI: 10.1787/9789264264885-en
[126] Food and Drug Administration, HHS. International Conference on Harmonisation; guidance on S2(R1) Genotoxicity Testing and Data Interpretation for Pharmaceuticals intended for Human Use; availability. Notice. Fed Regist. 2012 Jun 7;77(110):33748-9.
[127] Ames BN, Durston WE, Yamasaki E, Lee FD. Carcinogens are mutagens: a simple test system combining liver homogenates for activation and bacteria for detection. Proc Natl Acad Sci U S A. 1973 Aug;70(8):2281-5. DOI: 10.1073/pnas.70.8.2281
[128] Bhagat J. Combinations of genotoxic tests for the evaluation of group 1 IARC carcinogens. J Appl Toxicol. 2018;38:81-99. DOI: 10.1002/jat.3496
[129] Gupta P, Mathur N, Bhatnagar P, Nagar P, Srivastava S. Genotoxicity evaluation of hospital wastewaters. Ecotoxicol Environ Saf. 2009 Oct;72(7):1925-32. DOI: 10.1016/j.ecoenv.2009.05.012
[130] Dugan OM. Salmonella typhimurium as a test system for detecting the mutagenic activity of environmental pollutants. Cytol Genet. 1994;28(3):37-41.
[131] Dugan OM. Total mutagenic activity as an integral indicator of the assessment of the ecological and genetic state of the environment [dissertation abstract]. Kyiv: Ukrainian Scientific Hygienic Center; 1998. 39 p.
[132] Vijay U, Gupta S, Mathur P, Suravajhala P, Bhatnagar P. Microbial mutagenicity assay: Ames test. Bio Protoc. 2018 Mar 20;8(6):e2763. DOI: 10.21769/BioProtoc.2763
[133] Theis K, Skorvaga M, Machius M, Nakagawa N, Van Houten B, Kisker C. The nucleotide excision repair protein UvrB, a helicase-like enzyme with a catch. Mutat Res. 2000 Aug 30;460(3-4):277-300. DOI: 10.1016/s0921-8777(00)00032-x
[134] Simmon VF, Kauhanen K, Tardiff RG. Mutagenic activity of chemicals identified in drinking water. In: Scott D, Bridges BA, Sobels FH, editors. Progress in genetic toxicology. Vol. 2, Development in toxicology and environmental science. Amsterdam: Elsevier; 1977. pp. 249-58.
[135] Ames BN, Mccann J, Yamasaki E. Methods for detecting carcinogens and mutagens with the Salmonella/mammalian-microsome mutagenicity test. Mutat Res. 1975 Dec;31(6):347-64. DOI: 10.1016/0165-1161(75)90046-1
[136] Maron DM, Ames BN. Revised methods for the Salmonella mutagenicity test. Mutat Res. 1983 May;113(3-4):173-215. DOI: 10.1016/0165-1161(83)90010-9
[137] Zeiger E, Anderson B, Haworth S, Lawlor T, Mortelmans K. Salmonella mutagenicity tests: V. Results from the testing of 311 chemicals. Environ Mol Mutagen. 1992;19 Suppl 21:2-141. DOI: 10.1002/em.2850190603

[138] Wilcox P, Naidoo A, Wedd DJ, Gatehouse DG. Comparison of Salmonella typhimurium TA102 with Escherichia coli WP2 tester strains. Mutagenesis. 1990 May;5(3):285-91. DOI: 10.1093/mutage/5.3.285

[139] Nesslany F. The current limitations of in vitro genotoxicity testing and their relevance to the in vivo situation. Food Chem Toxicol. 2017;106(Pt B):609-15. DOI: 10.1016/j.fct.2016.08.035

[140] Hong YH, Jeon HL, Ko KY, Kim J, Yi JS, Ahn I, et al. Assessment of the predictive capacity of the optimized in vitro comet assay using HepG2 cells. Mutat Res. 2018;827:59-67. DOI: 10.1016/j.mrgentox.2018.01.010

[141] Cox JA, Fellows MD, Hashizume T, White PA. The utility of metabolic activation mixtures containing human hepatic post-mitochondrial supernatant (S9) for in vitro genetic toxicity assessment. Mutagenesis. 2016;31:117-30. DOI: 10.1093/mutage/gev082

[142] Vlach M, Quesnot N, Dubois-Pot-Schneider H, Ribault C, Verres Y, Petitjean K, et al. Cytochrome P450 1A1/2, 2B6 and 3A4 HepaRG cell-based biosensors to monitor hepatocyte differentiation, drug metabolism and toxicity. Sensors (Basel). 2019 May 15;19(10):2245. DOI: 10.3390/s19102245

[143] Benigni R, Bossa C, Tcheremenskaia O, Battistelli Cl, Crettaz P. The new ISSMIC database on in vivo micronucleus and its role in assessing genotoxicity testing strategies. Mutagenesis. 2012;27(1):87-92. DOI: 10.1093/mutage/ger064

[144] Soeteman-Hernández LG, Johnson GE, Slob W. Estimating the carcinogenic potency of chemicals from the in vivo micronucleus test. Mutagenesis. 2016;31(3):347-58. DOI: 10.1093/mutage/gev043

[145] Farabaugh CS, Doak S, Roy S, Elespuru R. In vitro micronucleus assay: Method for assessment of nanomaterials using cytochalasin B. Front Toxicol. 2023 Apr 26;5:1171960. DOI: 10.3389/ftox.2023.1171960

[146] Rodrigues MA, Probst CE, Zayats A, Davidson B, Riedel M, Li Y, Venkatachalam V. The in vitro micronucleus assay using imaging flow cytometry and deep learning. NPJ Syst Biol Appl. 2021 May 18;7(1):20. DOI: 10.1038/s41540-021-00179-5

[147] Hintzsche H, Hemmann U, Poth A, Utesch D, Lott J, Stopper H; Working Group "In vitro micronucleus test", Gesellschaft für Umwelt-Mutationsforschung (GUM, German-speaking section of the European Environmental Mutagenesis and Genomics Society EEMGS). Fate of micronuclei and micronucleated cells. Mutat Res Rev Mutat Res. 2017 Jan-Mar;771:85-98. DOI: 10.1016/j.mrrev.2017.02.002

[148] Fenech M. Commentary on the SFTG international collaborative study on the in vitro micronucleus test: to Cyt-B or not to Cyt-B? Mutat Res. 2006 Aug 4;607(1):9-12. DOI: 10.1016/j.mrgentox.2006.04.009

[149] Fenech M. A mathematical model of the in vitro micronucleus assay predicts false negative results if micronuclei are not specifically scored in binucleated cells or in cells that have completed one nuclear division. Mutagenesis. 2000 Jul;15(4):329-36. DOI: 10.1093/mutage/15.4.329

[150] Rodrigues MA. Automation of the in vitro micronucleus assay using the Imagestream® imaging flow cytometer. Cytometry A. 2018 Jul;93(7):706-26. DOI: 10.1002/cyto.a.23493

[151] Guan D, Fan K, Spence I, Matthews S. Combining machine learning models of in vitro and in vivo bioassays improves rat carcinogenicity prediction. Regul Toxicol Pharmacol. 2018 Apr;94:8-15. DOI: 10.1016/j.yrtph.2018.01.008

[152] Clare G. The in vitro mammalian chromosome aberration test. Methods Mol Biol. 2012;817:69-91. DOI: 10.1007/978-1-61779-421-6_5

[153] Obe G, Pfeiffer P, Savage JR, Johannes C, Goedecke W, Jeppesen P, et al. Chromosomal aberrations: formation, identification and distribution. Mutat Res. 2002 Jul 25;504(1-2):17-36. DOI: 10.1016/s0027-5107(02)00076-3

[154] Galloway SM, Armstrong MJ, Reuben C, Colman S, Brown B, Cannon C, et al. Chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cells: evaluations of 108 chemicals. Environ Mol Mutagen. 1987;10(S 10):1-35. DOI: 10.1002/em.2850100502

[155] Muehlbauer PA, Spellman RA, Gunther WC, Sanok KE, Wiersch CJ, O'Lone SD, et al. Improving dose selection and identification of aneugens in the in vitro chromosome aberration test by integration of flow cytometry-based methods. Environ Mol Mutagen. 2008 May;49(4):318-27. DOI: 10.1002/em.20387

[156] Galloway SM, Sofuni T, Shelby MD, Thilagar A, Kumaroo V, Kaur P, et al. Multilaboratory comparison of in vitro tests for chromosome aberrations in CHO and CHL cells tested under the same protocols. Environ Mol Mutagen. 1997;29(2):189-207. DOI: 10.1002/(SICI)1098-2280(1997)29:2<189::AID-EM10>3.0.CO;2-A

[157] Shelby MD, Sofuni T. Toxicology testing requirements and the U.S.-Japan collaborative study on in vitro tests for chromosomal aberrations. Environ Health Perspect. 1991 Aug;94:255-9. DOI: 10.1289/ehp.94-1567941

[158] Johannes C, Obe G. Chromosomal aberration test in human lymphocytes. Methods Mol Biol. 2013;1044:165-78. DOI: 10.1007/978-1-62703-529-3_8

[159] Ryu TH, Kim JH, Kim JK. Chromosomal aberrations in human peripheral blood lymphocytes after exposure to ionizing radiation. Genome Integr. 2016 Dec 30;7:5. DOI: 10.4103/2041-9414.197172

[160] Pei H, Fu HY, Hirai H, Cho DS, O'Brien TD, Dutton J, et al. Generation of induced pluripotent stem cells from Chinese hamster embryonic fibroblasts. Stem Cell Res. 2017 May;21:132-6. DOI: 10.1016/j.scr.2017.04.010

[161] Boffetta P, van der Hel O, Norppa H, Fabianova E, Fucic A, Gundy S, et al. Chromosomal aberrations and cancer risk: results of a cohort study from Central Europe. Am J Epidemiol. 2007 Jan 1;165(1):36-43. DOI: 10.1093/aje/kwj367

[162] Morita T, Nagaki T, Fukuda I, Okumura K. Clastogenicity of low pH to various cultured mammalian cells. Mutat Res. 1992 Aug;268(2):297-305. DOI: 10.1016/0027-5107(92)90235-t

[163] Long LH, Kirkland D, Whitwell J, Halliwell B. Different cytotoxic and clastogenic effects of epigallocatechin gallate in various cell-culture media due to variable rates of its oxidation in the culture medium. Mutat Res. 2007 Dec 1;634(1-2):177-83. DOI: 10.1016/j.mrgentox.2007.07.009

[164] Proudlock R, editor. Genetic toxicology testing. Boston: Academic Press; 2016. 1008 p. DOI: 10.1016/C2013-0-18870-8

[165] Rieder CL, Palazzo RE. Colcemid and the mitotic cycle. J Cell Sci. 1992 Jul;102 (Pt 3):387-92. DOI: 10.1242/jcs.102.3.387

[166] Nolasco S, Bellido J, Serna M, Carmona B, Soares H, Zabala JC. Colchicine blocks tubulin heterodimer recycling by tubulin cofactors TBCA, TBCB, and TBCE. Front Cell Dev Biol. 2021 Apr 22;9:656273. DOI: 10.3389/fcell.2021.656273

[167] Chen L, Li N, Liu Y, Faquet B, Alépée N, Ding C, et al. A new 3D model for genotoxicity assessment: EpiSkin™ Micronucleus Assay. Mutagenesis. 2021 Apr 28;36(1):51-61. DOI: 10.1093/mutage/geaa003

[168] Chung YH, Gulumian M, Pleus RC, Yu IJ. Animal welfare considerations when conducting OECD test guideline inhalation and toxicokinetic studies for nanomaterials. Animals (Basel). 2022 Nov 26;12(23):3305. DOI: 10.3390/ani12233305

[169] Jain AK, Pandey AK. In vivo micronucleus assay in mouse bone marrow. Methods Mol Biol. 2019;2031:135-46. DOI: 10.1007/978-1-4939-9646-9_7

[170] Morita T, MacGregor JT, Hayashi M. Micronucleus assays in rodent tissues other than bone marrow. Mutagenesis. 2011 Jan;26(1):223-30. DOI: 10.1093/mutage/geq066

[171] Hayashi M. The micronucleus test-most widely used in vivo genotoxicity test. Genes Environ. 2016 Oct 1;38:18. DOI: 10.1186/s41021-016-0044-x

[172] Dertinger SD, Miller RK, Brewer K, Smudzin T, Torous DK, Roberts DJ, et al. Automated human blood micronucleated reticulocyte measurements for rapid assessment of chromosomal damage. Mutat Res. 2007 Jan 10;626(1-2):111-9. DOI: 10.1016/j.mrgentox.2006.09.003

[173] Dertinger SD, Torous DK, Hayashi M, MacGregor JT. Flow cytometric scoring of micronucleated erythrocytes: an efficient platform for assessing in vivo cytogenetic damage. Mutagenesis. 2011 Jan;26(1):139-45. DOI: 10.1093/mutage/geq055

[174] Styles JA, Clark H, Festing MF, Rew DA. Automation of mouse micronucleus genotoxicity assay by laser scanning cytometry. Cytometry. 2001 Jun 1;44(2):153-5. DOI: 10.1002/1097-0320(20010601)44:2<153::aid-cyto1095>3.0.co;2-h

[175] Parton JW, Hoffman WP, Garriott ML. Validation of an automated image analysis micronucleus scoring system. Mutat Res. 1996 Aug;370(1):65-73. DOI: 10.1016/s0165-1218(96)90128-7

[176] Shibai-Ogata A, Tahara H, Yamamoto Y, Fujita M, Satoh H, Yuasa A, Hioki T, Kasahara T. An automated new technique for scoring the in vivo micronucleus assay with image analysis. Mutagenesis. 2014;29(1):63-71. DOI: 10.1093/mutage/get064

[177] European Medicine Agency. International conference on harmonization (ICH) of technical requirements for registration of pharmaceuticals for human use; ICH S2 (R1) Genotoxicity testing and data interpretation for pharmaceuticals intended for human use - Scientific guideline. EMA; 2011. 28 p.

[178] Araldi RP, de Melo TC, Mendes TB, de Sá Júnior PL, Nozima BH, Ito ET, et al. Using the comet and micronucleus assays for genotoxicity studies: A review. Biomed Pharmacother. 2015 May;72:74-82. DOI: 10.1016/j.biopha.2015.04.004

[179] Frötschl R. Experiences with the in vivo and in vitro comet assay in regulatory testing. Mutagenesis. 2015 Jan;30(1):51-7. DOI: 10.1093/mutage/geu069

[180] Møller P. The comet assay: ready for 30 more years. Mutagenesis. 2018 Feb 24;33(1):1-7. DOI: 10.1093/mutage/gex046

[181] Azqueta A, Ladeira C, Giovannelli L, Boutet-Robinet E, Bonassi S, Neri M, et al. Application of the comet assay in human biomonitoring: An hCOMET perspective. Mutat Res Rev Mutat Res. 2020 Jan-Mar;783:108288. DOI: 10.1016/j.mrrev.2019.108288

[182] Kitamoto S, Matsuyama R, Uematsu Y, Ogata K, Ota M, Yamada T, et al. Genotoxicity evaluation of benzene, di(2-ethylhexyl) phthalate, and trisodium ethylenediamine tetraacetic acid monohydrate using a combined rat comet/micronucleus assays. Mutat Res Genet Toxicol Environ Mutagen. 2015 Jul;786-788:137-43. DOI: 10.1016/j.mrgentox.2015.05.002.

[183] Medrano-Padial C, Puerto M, Prieto AI, Ayala N, Beaumont P, Rouger C, et al. In vivo genotoxicity evaluation of a stilbene extract prior to its use as a natural additive: A combination of the micronucleus test and the comet assay. Foods. 2021 Feb 17;10(2):439. DOI: 10.3390/foods10020439

[184] Møller P, Azqueta A, Boutet-Robinet E, Koppen G, Bonassi S, Milić M, et al. Minimum information for reporting on the comet assay (MIRCA): recommendations for describing comet assay procedures and results. Nat Protoc. 2020 Dec;15(12):3817-26. DOI: 10.1038/s41596-020-0398-1

[185] Subash P. Assessment of oxidative DNA damage by alkaline comet assay in human essential hypertension. Indian J Clin Biochem. 2016;31(2):185-93. DOI: 10.1007/s12291-015-0521-1

[186] Corredor Z, Rodríguez-Ribera L, Silva I, Díaz JM, Ballarín J, Marcos R, et al. Levels of DNA damage in peripheral blood lymphocytes of patients undergoing standard hemodialysis vs on-line hemodiafiltration: A comet assay investigation. Mutat Res Genet Toxicol Environ Mutagen. 2016 Sep 15;808:1-7. DOI: 10.1016/j.mrgentox.2016.07.008

[187] Pittaluga M, Sgadari A, Dimauro I, Tavazzi B, Parisi P, Caporossi D. Physical exercise and redox balance in type 2 diabetics: effects of moderate training on biomarkers of oxidative stress and DNA damage evaluated through comet assay. Oxid Med Cell Longev. 2015;2015:981242. DOI: 10.1155/2015/981242

[188] Dhar G, Mishra M. Comet assay to detect the severity of DNA damage in drosophila. In: Mishra M, editor. Fundamental approaches to screen abnormalities in Drosophila. Springer Protocols Handbooks. New York: Springer; 2020. DOI: 10.1007/978-1-4939-9756-5_8

[189] Tahara H, Yamagiwa Y, Haranosono Y, Kurata M. In vivo comet assay in rabbit corneal epithelial cells following ocular instillation with genotoxic compounds. Genes Environ. 2021 Apr 7;43(1):11. DOI: 10.1186/s41021-021-00184-4

[190] Gyori BM, Venkatachalam G, Thiagarajan PS, Hsu D, Clement MV. OpenComet: an automated tool for comet assay image analysis. Redox Biol. 2014 Jan 9;2:457-65. DOI: 10.1016/j.redox.2013.12.020

[191] Lee T, Lee S, Sim WY, Jung YM, Han S, Won JH, et al. HiComet: a high-throughput comet analysis tool for large-scale DNA damage assessment. BMC Bioinformatics. 2018 Feb 19;19(Suppl 1):44. DOI: 10.1186/s12859-018-2015-7

[192] Li J, Beiser A, Dey NB, Takeda S, Saha LK, Hirota K, et al. A high-throughput 384-well CometChip platform reveals a role for 3-methyladenine in the cellular response to etoposide-induced DNA damage. NAR Genom Bioinform. 2022 Sep 13;4(3):lqac065. DOI: 10.1093/nargab/lqac065

[193] Beleon A, Pignatta S, Arienti C, Carbonaro A, Horvath P, Martinelli G, et al. CometAnalyser: A user-friendly, open-source deep-learning microscopy tool for quantitative comet assay analysis. Comput Struct Biotechnol J. 2022 Aug 3;20:4122-30. DOI: 10.1016/j.csbj.2022.07.053

[194] Ostling O, Johanson KJ. Microelectrophoretic study of radiation-induced DNA damages in individual mammalian cells. Biochem Biophys Res Commun. 1984 Aug 30;123(1):291-8. DOI: 10.1016/0006-291X(84)90411-X

[195] Corvi R, Madia F. In vitro genotoxicity testing-Can the performance be enhanced? Food Chem Toxicol. 2017 Aug;106(Pt B):600-8. DOI: 10.1016/j.fct.2016.08.024

[196] Pistollato F, Madia F, Corvi R, Munn S, Grignard E, Paini A, et al. Current EU regulatory requirements for the assessment of chemicals and cosmetic products: challenges and opportunities for introducing new approach methodologies. Arch Toxicol. 2021 Jun;95(6):1867-97. DOI: 10.1007/s00204-021-03034-y

[197] Fowler P, Smith K, Young J, Jeffrey L, Kirkland D, Pfuhler S, et al. Reduction of misleading ("false") positive results in mammalian cell genotoxicity assays. I. Choice of cell type. Mutat Res. 2012;742(1-2):11-25. DOI: 10.1016/j.mrgentox.2011.10.014

[198] Kirkland D, Pfuhler S, Tweats D, Aardema M, Corvi R, Darroudi F, et al. How to reduce false positive results when undertaking in vitro genotoxicity testing and thus avoid unnecessary follow-up animal tests: Report of an ECVAM Workshop. Mutat Res. 2007 Mar 30;628(1):31-55. DOI: 10.1016/j.mrgentox.2006.11.008

[199] Choudhuri S, Patton GW, Chanderbhan RF, Mattia A, Klaassen CD. From classical toxicology to Tox21: Some critical conceptual and technological advances in the molecular understanding of the toxic response beginning from the last quarter of the 20th century. Toxicol Sci. 2018 Jan 1;161(1):5-22. DOI: 10.1093/toxsci/kfx186

[200] Krewski D, Andersen ME, Tyshenko MG, Krishnan K, Hartung T, Boekelheide K, et al. Toxicity testing in the 21st century: progress in the past decade and future perspectives. Arch Toxicol. 2020 Jan;94(1):1-58. DOI: 10.1007/s00204-019-02613-4

[201] Guan D, Fan K, Spence I, Matthews S. Combining machine learning models of in vitro and in vivo bioassays improves rat carcinogenicity prediction. Regul Toxicol Pharmacol. 2018 Apr;94:8-15. DOI: 10.1016/j.yrtph.2018.01.008

[202] Mandon M, Huet S, Dubreil E, Fessard V, Le Hégarat L. Three-dimensional HepaRG spheroids as a liver model to study human genotoxicity in vitro with the single cell gel electrophoresis assay. Sci Rep. 2019;9(1):10548. DOI: 10.1038/s41598-019-47114-7

[203] Štampar M, Sedighi Frandsen H, Rogowska-Wrzesinska A, Wrzesinski K, Filipič M, et al. Hepatocellular carcinoma (HepG2/C3A) cell-based 3D model for genotoxicity testing of chemicals. Sci Total Environ. 2021 Feb 10;755(Pt 2):143255. DOI: 10.1016/j.scitotenv.2020.143255

[204] Waldherr M, Mišík M, Ferk F, Tomc J, Žegura B, Filipič M, et al. Use of HuH6 and other human-derived hepatoma lines for the detection of genotoxins: a new hope for laboratory animals? Arch Toxicol. 2018;92(2):921-34. DOI: 10.1007/s00204-017-2109-4

[205] Smart DJ, Helbling FR, Verardo M, Huber A, McHugh D, Vanscheeuwijck P. Development of an integrated assay in human TK6 cells to permit comprehensive genotoxicity analysis in vitro. Mutat Res Genet Toxicol Environ Mutagen. 2020 Jan;849:503129. DOI: 10.1016/j.mrgentox.2019.503129

[206] Collins PL, Purman C, Porter SI, Nganga V, Saini A, Hayer KE, et al. DNA double-strand breaks induce H2Ax phosphorylation domains in a contact-dependent manner. Nat Commun. 2020 Jun 22;11(1):315. DOI: 10.1038/s41467-020-16926-x

[207] Rahmanian N, Shokrzadeh M, Eskandani M. Recent advances in γH2AX biomarker-based genotoxicity assays: A marker of DNA damage and repair. DNA Repair (Amst). 2021 Dec;108:103243. DOI: 10.1016/j.dnarep.2021.103243

[208] Matsuoka S, Ballif BA, Smogorzewska A, McDonald ER 3rd, Hurov KE, Luo J, et al. ATM and ATR substrate analysis reveals extensive protein networks responsive to DNA damage. Science. 2007;316(5828):1160-6. DOI: 10.1126/science.1140321

[209] Bonner WM, Redon CE, Dickey JS, Nakamura AJ, Sedelnikova OA, Solier S, et al. GammaH2AX and cancer. Nat Rev Cancer. 2008 Dec;8(12):957-67. DOI: 10.1038/nrc2523

[210] Mah LJ, El-Osta A, Karagiannis TC. gammaH2AX: a sensitive molecular marker of DNA damage and repair. Leukemia. 2010 Apr;24(4):679-86. DOI: 10.1038/leu.2010.6

[211] Reddig A, Roggenbuck D, Reinhold D. Comparison of different immunoassays for γH2AX quantification. J Lab Precis Med 2018;3:80. DOI: 10.21037/jlpm.2018.09.01

[212] Boisvert L, Derr R, Osterlund T, Hendriks G, Brandsma I. Quantitative interpretation of ToxTracker dose-response data for potency comparisons and mode-of-action determination. Environ Mol Mutagen. 2023;64(2):132-43. DOI: 10.1002/em.22525

[213] Hendriks G, Derr RS, Misovic B, Morolli B, Calléja FM, Vrieling H. The extended ToxTracker assay discriminates between induction of DNA damage, oxidative stress, and protein misfolding. Toxicol Sci. 2016;150(1):190-203. DOI: 10.1093/toxsci/kfv323

[214] Araten DJ, Nafa K, Pakdeesuwan K, Luzzatto L. Clonal populations of hematopoietic cells with paroxysmal nocturnal hemoglobinuria genotype and phenotype are present in normal individuals. Proc Natl Acad Sci U S A. 1999 Apr 27;96(9):5209-14. DOI: 10.1073/pnas.96.9.5209

[215] Organisation for Economic Co-operation and Development (OECD). Test No. 470: Mammalian Erythrocyte Pig-a Gene Mutation Assay. In: OECD Guidelines for the Testing of Chemicals, Section 4. Paris: OECD Publishing; 2016. DOI: 10.1787/4faea90e-en

[216] Kawagoe K, Takeda J, Endo Y, Kinoshita T. Molecular cloning of murine pig-a, a gene for GPI-anchor biosynthesis, and demonstration of interspecies conservation of its structure, function, and genetic locus. Genomics. 1994 Oct;23(3):566-74. DOI: 10.1006/geno.1994.1544

[217] Brodsky RA, Hu R. PIG-A mutations in paroxysmal nocturnal hemoglobinuria and in normal hematopoiesis. Leuk Lymphoma. 2006 Jul;47(7):1215-21. DOI: 10.1080/10428190600555520

[218] Cross GA. Glycolipid anchoring of plasma membrane proteins. Annu Rev Cell Biol. 1990;6:1-39. DOI: 10.1146/annurev.cb.06.110190.000245

[219] Kimoto T, Horibata K, Miura D, Chikura S, Okada Y, Ukai A, et al. The PIGRET assay, a method for measuring Pig-a gene mutation in reticulocytes, is reliable as a short-term in vivo genotoxicity test: Summary of the MMS/JEMS-collaborative study across 16 laboratories using 24 chemicals. Mutat Res Genet Toxicol Environ Mutagen. 2016 Nov 15;811:3-15. DOI: j.mrgentox.2016.10.003

[220] Cao Y, Wang T, Xi J, Zhang G, Wang T, Liu W, et al. PIG-A gene mutation as a genotoxicity biomarker in human population studies: An investigation in lead-exposed workers. Environ Mol Mutagen. 2020 Jul;61(6):611-21. DOI: 10.1002/em.22373

[221] Cao Y, Wang X, Liu W, Feng N, Xi J, You X, et al. The potential application of human PIG-A assay on azathioprine-treated inflammatory bowel disease patients. Environ Mol Mutagen. 2020 Apr;61(4):456-64. DOI: 10.1002/em.22348

[222] Reisinger K, Dony E, Wolf T, Maul K. Hen's egg test for micronucleus induction (HET-MN). Methods Mol Biol. 2019;2031:195-208. DOI: 10.1007/978-1-4939-9646-9_10

[223] Reisinger K, Fieblinger D, Heppenheimer A, Kreutz J, Liebsch M, Luch A, et al. The hen's egg test for micronucleus induction (HET-MN): validation data set. Mutagenesis. 2022 May 4;37(2):61-75. DOI: 10.1093/mutage/geab016

[224] Valentine CC 3rd, Young RR, Fielden MR, Kulkarni R, Williams LN, Li T, et al. Direct quantification of in vivo mutagenesis and carcinogenesis using duplex sequencing. Proc Natl Acad Sci U S A. 2020;117(52):33414-25. DOI: 10.1073/pnas.2013724117

[225] Salk JJ, Schmitt MW, Loeb LA. Enhancing the accuracy of next-generation sequencing for detecting rare and subclonal mutations. Nat Rev Genet. 2018 May;19(5):269-285. DOI: 10.1038/nrg.2017.117

[226] Menz J, Götz ME, Gündel U, Gürtler R, Herrmann K, Hessel-Pras S, et al. Genotoxicity assessment: opportunities, challenges and perspectives for quantitative evaluations of dose-response data. Arch Toxicol. 2023 Sep;97(9):2303-28. DOI: 10.1007/s00204-023-03553-w

[227] Bae JH, Liu R, Roberts E, Nguyen E, Tabrizi S, Rhoades J, et al. Single duplex DNA sequencing with CODEC detects mutations with high sensitivity. Nat Genet. 2023 May;55(5):871-79. DOI: 10.1038/s41588-023-01376-0

[228] Barylyak IR, Dugan O.M. Ecological and genetic research in Ukraine. Cytol Genet. 2002;5:3-10.

[229] Yalovenko OI, Dugan OM. Potential mutagenic effect of hair dye ingredients in alternative test systems. Probl Environ Med Genet Clin Immunol. 2006;1:34-47.

[230] Wichard JD. In silico prediction of genotoxicity. Food Chem Toxicol. 2017 Aug;106(Pt B):595-9. DOI: 10.1016/j.fct.2016.12.013

[231] Cavasotto CN, Scardino V. Machine learning toxicity prediction: Latest advances by toxicity end point. ACS Omega. 2022 Dec 13;7(51):47536-46. DOI: 10.1021/acsomega.2c05693

[232] Yuan Q, Wei Z, Guan X, Jiang M, Wang S, Zhang S, et al. Toxicity prediction method based on multi-channel convolutional neural network. Molecules. 2019 Sep 17;24(18):3383. DOI: 10.3390/molecules24183383

[233] Soares TA, Nunes-Alves A, Mazzolari A, Ruggiu F, Wei GW, Merz K. The (Re)-evolution of quantitative structure-activity relationship (QSAR) studies propelled by the surge of machine learning methods. J Chem Inf Model. 2022 Nov 28;62(22):5317-20. DOI: 10.1021/acs.jcim.2c01422

[234] Keyvanpour MR, Shirzad MB. An analysis of QSAR research based on machine learning concepts. Curr Drug Discov Technol. 2021;18(1):17-30. DOI: 10.2174/1570163817666200316104404

[235] Yang X, Zhang Z, Li Q, Cai Y. Quantitative structure-activity relationship models for genotoxicity prediction based on combination evaluation strategies for toxicological alternative experiments. Sci Rep. 2021;11(1):8030. DOI: 10.1038/s41598-021-87035-y

[236] Lou C, Yang H, Deng H, Huang M, Li W, Liu G, Lee PW, Tang Y. Chemical rules for optimization of chemical mutagenicity via matched molecular pairs analysis and machine learning methods. J Cheminform. 2023 Mar 20;15(1):35. DOI: 10.1186/s13321-023-00707-x

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СИСТЕМИ ГЕНЕТИЧНОЇ ОЦІНКИ ВПЛИВУ ФАКТОРІВ НАВКОЛИШНЬОГО СЕРЕДОВИЩА

Однією з важливих складових частин охорони довкілля є розроблення гігієнічних нормативів, що дають змогу захистити популяцію людини від несприятливого впливу забруднення природи шкідливими речовинами. Європейським і американським хімічними товариствами були представлені приблизно 800 тис. хімічних речовин, для яких на сьогодні відсутня інформація щодо потенційних ризиків для генетичної складової здоров'я людини та негативного впливу на довкілля. В умовах експоненційного збільшення хімічних сполук, що генерує людство в різних сферах виробництва, особливо актуальною є проблема ефективного виявлення та обліку різноманітних факторів генетичної та канцерогенної небезпеки. Оцінка потенційної генотоксичності факторів навколишнього середовища є невід'ємною складовою оцінки генетичної безпеки з урахуванням як прокаріотичних, так і еукаріотичних організмів включно з людиною. Оцінка генетичної активності хімічних сполук є базовою вимогою для проведення їх всебічної токсикологічної оцінки. У представленому огляді, з точки зору генетичних та епігенетичних механізмів впливу, розглянуто стандартні методи виявлення й оцінки потенціальної генетичної небезпеки факторів довікілля, що відносяться до стандартної, загальноприйнятої батареї тест-систем, а також деякі сучасні експериментальні методи, що не є на сьогодні масово визнаними. Проведено детальний аналіз підходів щодо оцінки потенційної генетичної мутагенної активності. Показані їхні основні переваги та недоліки. З урахуванням рекомендацій Організації економічного співробітництва та розвитку щодо проведення тестування небезпечних хімічних сполук, які можуть впливати на здоров'я людини, зроблено спробу пошуку оптимальних підходів для вирішення задачі прогнозування генетичних ефектів та їхніх наслідків для людини.

Ключові слова: геном; пошкодження дезоксирибонуклеїнової кислоти; генотоксичність; канцерогенез; мутагенез; тест-система мутацій.