

NC3Rs Toxicology and Regulatory Sciences Bibliography and Resources

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An introduction to the NC3Rs and an overview of our office-led programmes of work in Toxicology and Regulatory Sciences can be found in the *Journal of the American Association for Laboratory Animal Science*:

- Burden N, Chapman K, Sewell F, Robinson V (2015). Pioneering better science through the 3Rs: An introduction to the National Centre for the Replacement, Refinement, and Reduction of Animals in Research (NC3Rs). *Journal of the American Association for Laboratory Animal Science* 54(2): 198-208. No DOI: available to download at www.ncbi.nlm.nih.gov/pmc/articles/PMC4382625.

Pioneering Better Science



Web-based resources

Web resource 'hubs' pull together information, publications and guidance in specific areas that have resulted from NC3Rs office-led projects:

- Animals in chemical safety testing:
www.nc3rs.org.uk/animals-chemical-safety-testing
- Animals in environmental safety testing:
www.nc3rs.org.uk/animals-environmental-safety-testing
- Animals in drug discovery and development:
www.nc3rs.org.uk/animals-drug-discovery-and-development

Resource webpages focus on key aspects of our projects:

- Pathways-based approaches resource page:
www.nc3rs.org.uk/pathways-based-approaches-resource-page
Supports scientists and regulators interested in developing and applying pathways-based/mechanistic approaches for safety assessment. As part of this resource we provide a regular periodical called Adverse Outcome Pathway (AOP) News, which aims to keep interested parties updated on the latest information and opportunities related to pathways-based approaches and AOPs.
- Microsampling resource page:
www.nc3rs.org.uk/microsampling
Provides guidance on using microsampling in toxicology studies.

1. Animals in chemical safety assessment

1.1 Non-animal approaches and chemical safety assessment

- Prior H, Casey W, Kimber I, Whelan M, Sewell F (2019). Reflections on the progress towards non-animal methods for acute toxicity testing of chemicals. *Regulatory Toxicology and Pharmacology* 102 30-33. DOI: [10.1016/j.yrtph.2018.12.008](https://doi.org/10.1016/j.yrtph.2018.12.008).
- Sewell F, Doe J, Gellatly N, Ragan I, Burden N (2017). Steps towards the international regulatory acceptance of non-animal methodology in safety assessment. *Regulatory Toxicology and Pharmacology* 89: 50-56. DOI: [10.1016/j.yrtph.2017.07.001](https://doi.org/10.1016/j.yrtph.2017.07.001).
- Burden N, Sewell F, Chapman K (2015). Testing chemical safety: What is needed to ensure the widespread application of non-animal approaches? *PLoS Biology* 13(5): e1002156. DOI: [10.1371/journal.pbio.1002156](https://doi.org/10.1371/journal.pbio.1002156).
- Burden N, Mahony C, Müller BP, Terry C, Westmoreland C, Kimber I (2015). Aligning the 3Rs with new paradigms in the safety assessment of chemicals. *Toxicology* 330: 62-66. DOI: [10.1016/j.tox.2015.01.014](https://doi.org/10.1016/j.tox.2015.01.014).
- Rivetti C, Allen T, Brown J, Butler E, Carmichael P, Colbourne J, Dent M, Falciani F, Gunnarsson L, Gutsell S, Harrill J, Hodges G, Jennings P, Judson R, Kienzler A, Margiotta-Casaluci L, Muller, I., Owen, S., Rendal C, Russell P, Scott S, Sewell F, Shah I, Sorrel I, Viant M, Westmoreland C, White A, Campos B. (2019). Vision of a near future: Bridging the human health–environment divide. Toward an integrated strategy to understand mechanisms across species for chemical safety assessment. *Toxicology in Vitro*, 62, p.104692. DOI: [10.1016/j.tiv.2019.104692](https://doi.org/10.1016/j.tiv.2019.104692)

1.2 Redundancy in acute toxicity testing

- Moore NP, Andrew DJ, Bjerke DL, Creton S, Dreher D, Holmes T, Prieto P, Seidle T, Rowan TG (2013). Can acute dermal systemic toxicity tests be replaced with oral tests? A comparison of route-specific systemic toxicity and hazard classifications under the Globally Harmonized System of Classification and Labelling of Chemicals (GHS). *Regulatory Toxicology and Pharmacology* 66(1): 30-37. DOI: [10.1016/j.yrtph.2013.02.005](https://doi.org/10.1016/j.yrtph.2013.02.005).
- Creton S, Dewhurst IC, Earl LK, Gehen SC, Guest RL, Hotchkiss JA, Indans I, Woolhiser MR, Billington R (2010). Acute toxicity testing of chemicals – Opportunities to avoid redundant testing and use alternative approaches. *Critical Reviews in Toxicology* 40: 50-83. DOI: [10.3109/10408440903401511](https://doi.org/10.3109/10408440903401511).
- Chapman K, Creton S, Kupferschmidt H, Bond GR, Wilks MF, Robinson S (2010). The value of acute toxicity studies to support the clinical management of overdose and poisoning: A cross-discipline consensus. *Regulatory Toxicology and Pharmacology* 58: 354-359. DOI: [10.1016/j.yrtph.2010.07.003](https://doi.org/10.1016/j.yrtph.2010.07.003).
- Holmes AM, Creton S, Chapman K (2010). Working in partnership to advance the 3Rs in toxicity testing. *Toxicology* 267(1-3): 14-19. DOI: [10.1016/j.tox.2009.11.006](https://doi.org/10.1016/j.tox.2009.11.006).

- Seidle T, Robinson S, Holmes T, Creton S, Prieto P, Scheel J, Chlebus M (2010). Cross-sector review of drivers and available 3Rs approaches for acute systemic toxicity testing. *Toxicological Sciences* 116(2): 382-396. DOI: [10.1093/toxsci/kfq143](https://doi.org/10.1093/toxsci/kfq143).
- NC3Rs Leaflet: Acute toxicity testing of chemicals: opportunities to avoid redundant testing and use alternative approaches. Available to download at www.nc3rs.org.uk/redundancy-acute-toxicity-testing-chemicals.

1.3 Adoption of the Fixed Concentration Procedure (FCP) for acute inhalation studies

- Sewell F, Ragan I, Indans I, Marczylo T, Stallard N, Griffiths D, Holmes T, Smith P and Horgan G (2018). An evaluation of the fixed concentration procedure for assessment of acute inhalation toxicity. *Regulatory Toxicology and Pharmacology* 94: 22-32. DOI: [10.1016/j.yrtph.2018.01.001](https://doi.org/10.1016/j.yrtph.2018.01.001).
- OECD (2017). Test no. 433: Acute Inhalation Toxicity: Fixed Concentration Procedure. *OECD Publishing, Paris*. DOI: [10.1787/9789264284166-en](https://doi.org/10.1787/9789264284166-en).
- Sewell F, Ragan I, Marczylo T, Anderson B, Braun A, Casey W, Dennison N, Griffiths D, Guest R, Holmes T, van Huygevoort T, Indans I, Kenny T, Kojima H, Lee K, Prieto P, Smith P, Smedley J, Stokes WS, Wnorowski G, Horgan G (2015). A global initiative to refine acute inhalation studies through the use of 'evident toxicity' as an endpoint: towards adoption of the fixed concentration procedure. *Regulatory Toxicology and Pharmacology* 73(3): 770-779. DOI: [10.1016/j.yrtph.2015.10.018](https://doi.org/10.1016/j.yrtph.2015.10.018).
- Price C, Stallard N, Creton S, Indans I, Guest RL, Griffiths D, Edwards P (2011). A statistical evaluation of the effects of gender differences in assessment of acute inhalation toxicity. *Human and Experimental Toxicology* 30(3): 217-238. DOI: [10.1177/09603271110370982](https://doi.org/10.1177/09603271110370982).
- Stallard N, Price C, Creton S, Indans I, Guest RL, Griffiths D, Edwards P (2011). A new sighting study for the fixed concentration procedure to allow for gender differences. *Human and Experimental Toxicology* 30(3): 239-249. DOI: [10.1177/09603271110370983](https://doi.org/10.1177/09603271110370983).

1.4 Applying pathways-based approaches across the biosciences

- Sewell F, Gellatly N, Beaumont M, Burden N, Currie R, de Haan L, Hutchinson TH, Jacobs M, Mahony C, Malcomber I, Mehta J, Whale G, Kimber I (2018). The future trajectory of adverse outcome pathways: a commentary. *Archives of Toxicology* 92(4): 1657-1661. DOI: [10.1007/s00204-018-2183-2](https://doi.org/10.1007/s00204-018-2183-2).
- Burden N, Sewell F, Andersen ME, Boobis A, Chipman JK, Cronin MTD, Hutchinson TH, Kimber I, Whelan M (2015). Adverse Outcome Pathways can drive non-animal approaches for safety assessment. *Journal of Applied Toxicology* 35(9): 971-975. DOI: [10.1002/jat.3165](https://doi.org/10.1002/jat.3165).

1.5 Reducing animal use in the safety assessment of nanomaterials

- Burden N, Aschberger K, Chaudhry Q, Clift MJD, Doak SH, Fowler P, Johnston H, Landsiedel R, Rowland J, Stone V (2017). The 3Rs as a framework to support a 21st century approach for nanosafety assessment. *Nano Today* 12: 10-13. DOI: [10.1016/j.nantod.2016.06.007](https://doi.org/10.1016/j.nantod.2016.06.007).



- Burden N, Aschberger K, Chaudhry Q, Clift MJD, Fowler P, Johnston H, Landsiedel R, Rowland J, Stone V, Doak SH (2017). Aligning nanotoxicology with the 3Rs: What is needed to realise the short, medium and long-term opportunities? *Regulatory Toxicology and Pharmacology* 91: 257-266. DOI: [10.1016/j.yrtph.2017.10.021](https://doi.org/10.1016/j.yrtph.2017.10.021).

1.6 Toxicokinetics

- Creton S, Saghir SA, Bartels MJ, Billington R, Bus JS, Davies W, Dent MP, Hawksworth GM, Parry S, Travis KZ (2012). Use of toxicokinetics to support chemical evaluation: Informing high dose selection and study interpretation. *Regulatory Toxicology and Pharmacology* 62(2): 241-247. DOI: [10.1016/j.yrtph.2011.12.005](https://doi.org/10.1016/j.yrtph.2011.12.005).
- Creton S, Billington R, Davies W, Dent MP, Hawksworth GM, Parry S, Travis KZ (2009). Application of toxicokinetics to improve chemical risk assessment: Implications for the use of animals. *Regulatory Toxicology and Pharmacology* 55: 291-299. DOI: [10.1016/j.yrtph.2009.08.001](https://doi.org/10.1016/j.yrtph.2009.08.001).

1.7 Exposure-driven risk assessment

- Sewell F, Aggarwal M, Bachler G, Broadmeadow A, Gellatly N, Moore E, Robinson S, Rooseboom M, Stevens A, Terry C, Burden N (2017). The current status of exposure-driven approaches for chemical safety assessment: A cross-sector perspective. *Toxicology* 389: 109-117. DOI: [10.1016/j.tox.2017.07.018](https://doi.org/10.1016/j.tox.2017.07.018).
- NC3Rs/Unilever (2017). Workshop report: Applying exposure science to increase the utility of non-animal data in efficacy and safety testing. *NC3Rs, London*. Available to download at www.nc3rs.org.uk/applying-exposure-science-increase-utility-non-animal-data-efficacy-and-safety-testing.
- Rowbotham AL and Gibson RM (2011). Exposure-driven risk assessment: Applying exposure-based waiving of toxicity tests under REACH. *Food and Chemical Toxicology* 49(8): 1661-1673. DOI: [10.1016/j.fct.2011.03.050](https://doi.org/10.1016/j.fct.2011.03.050).

1.8 Non-animal methods for cosmetics testing

- Gellatly N and Sewell F (2019). Regulatory acceptance of in silico approaches for the safety assessment of cosmetic-related substances. *Computational Toxicology* 11: 82-89 DOI: [10.1016/j.comtox.2019.03.003](https://doi.org/10.1016/j.comtox.2019.03.003).
- Adler S, Basketter D, Creton S, Pelkonen O, van Benthem J, Zuang V, Andersen KE, Angers-Loustau A, Aptula A, Bal-Price A, Benfenati E, Bernauer U, Bessems J, Bois FY, Boobis A, Brandon E, Bremer S, Broschard T, Casati S, Coecke S, Corvi R, Cronin M, Daston G, Dekant W, Felter S, Grignard E, Gundert-Remy U, Heinonen T, Kimber I, Kleinjans J, Komulainen H, Kreiling R, Kreysa J, Leite SB, Loizou G, Maxwell G, Mazzatorta P, Munn S, Pfuhler S, Phrakonkham P, Piersma A, Poth A, Prieto P, Repetto G, Rogiers V, Schoeters G, Schwarz M, Serafimova R, Tähti H, Testai E, van Delft J, van Loveren H, Vinken M, Worth A, Zaldivar JM (2011). Alternative (non-animal) methods for cosmetics testing: current status and future prospects – 2010. *Archives of Toxicology* 85(5): 367-485. DOI: [10.1007/s00204-011-0693-2](https://doi.org/10.1007/s00204-011-0693-2).

1.9 *In vitro* approaches for carcinogenicity testing

- Creton S, Aardema MJ, Carmichael PL, Harvey JS, Martin FL, Newbold RF, O'Donovan MR, Pant K, Poth A, Sakai A, Sasaki K, Scott AD, Schechtman LM, Shen RR, Tanaka N, Yasaei H (2012). Cell transformation assays for prediction of carcinogenic potential: state of the science and future research needs. *Mutagenesis* 27(1): 93-101. DOI: [10.1093/mutage/ger053](https://doi.org/10.1093/mutage/ger053).

1.10 Bile duct cannulation

- Burden N, Kendrick J, Knight L, McGregor V, Murphy H, Punler M, van Wijk H (2017). Maximizing the success of bile duct cannulation studies in rats: recommendations for best practice. *Laboratory Animals* 51(5): 457-464. DOI: [10.1177/0023677217698001](https://doi.org/10.1177/0023677217698001).

1.11 *In silico* toxicology protocols

- Hasselgren C, Ahlberg E, Akahori Y, Amberg A, Anger L, Atienzar F, Auerbach S, Beilke L, Bellion P, Benigni R, Bercu J, Booth E, Bower D, Brigo A, Cammerer Z, Cronin M, Crooks I, Cross K, Custer L, Dobo K, Doktorova T, Faulkner D, Ford K, Fortin M, Frericks M, Gad-McDonald S, Gellatly N, Gerets H, Gervais V, Glowienke S, Van Gompel J, Harvey J, Hillegass J, Honma M, Hsieh J, Hsu C, Barton-Maclaren T, Johnson C, Jolly R, Jones D, Kemper R, Kenyon M, Kruhlak N, Kulkarni S, Kümmerer K, Leavitt P, Masten S, Miller S, Moudgal C, Muster W, Paulino A, Lo Piparo E, Powley M, Quigley D, Reddy M, Richarz A, Schilter B, Snyder R, Stavitskaya L, Stidl R, Szabo D, Teasdale A, Tice R, Trejo-Martin A, Vuorinen A, Wall B, Watts P, White A, Wichard J, Witt K, Woolley A, Woolley D, Zwickl C, Myatt, G. (2019). Genetic toxicology *in silico* protocol. *Regulatory Toxicology and Pharmacology*, 107: 104403. DOI: [10.1016/j.yrtph.2019.104403](https://doi.org/10.1016/j.yrtph.2019.104403).
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2. Animals in environmental safety assessment

2.1 Promoting the 3Rs in ecotoxicology

- Lagadic L, Bender K, Burden N, Salinas ER, Weltje L (2019). Recommendations for Reducing the Use of Fish and Amphibians in Endocrine-Disruption Testing of Biocides and Plant Protection Products in Europe. *Integrated Environmental Assessment and Management*, 15: 659-662. DOI: [10.1002/ieam.4156](https://doi.org/10.1002/ieam.4156).
- Burden N, Gellatly N, Benstead R, Benyon K, Blickley TM, Clook M, Doyle I, Edwards P, Handley J, Katsiadaki I, Lillicrap A, Mead C, Ryder K, Salinas E, Wheeler J, Hutchinson TH (2017). Reducing repetition of regulatory vertebrate ecotoxicology studies. *Integrated Environmental Assessment and Management* 13(5) 955-957. DOI: [10.1002/ieam.1934](https://doi.org/10.1002/ieam.1934).
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- Hutchinson TH, Wheeler JR, Gourmelon A, Burden N (2015). Promoting the 3Rs to enhance the OECD fish toxicity testing framework. *Regulatory Toxicology and Pharmacology* 76: 231-233. DOI: [10.1016/j.yrtph.2016.02.006](https://doi.org/10.1016/j.yrtph.2016.02.006).
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2.2 Assessing the need for chronic fish studies on formulated pesticides

- Creton S, Douglas M, Wheeler JR, Hutchinson TH (2010). Challenging the requirement for chronic fish toxicity studies on formulated plant protection products. *Toxicology Letters* 199(2): 111-114. DOI: [10.1016/j.toxlet.2010.08.019](https://doi.org/10.1016/j.toxlet.2010.08.019)

2.3 Applying the one concentration approach in fish bioaccumulation studies

- Burden N, Maynard SK, Weltje L, Wheeler JR, Doyle I, Clook M (2017). Reducing the number of fish in regulatory bioconcentration testing: Identifying and overcoming the barriers to using the 1-concentration approach. *Integrated Environmental Assessment and Management* 13(1): 212-214. DOI: [10.1002/ieam.1851](https://doi.org/10.1002/ieam.1851).
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2.4 Applying the threshold approach in fish acute toxicity studies

- Creton S, Clook M, Wheeler JR (2014). Application of the threshold approach for acute fish toxicity testing to plant protection products: a proposed framework. *Chemosphere* 96: 195-200. DOI: [10.1016/j.chemosphere.2013.10.015](https://doi.org/10.1016/j.chemosphere.2013.10.015).

2.5 Using QSARs to predict fish acute toxicity of pesticide metabolites

- Burden N, Maynard SK, Weltje L, Wheeler JR (2016). The utility of QSARs in predicting acute fish toxicity of pesticide metabolites: A retrospective validation approach. *Regulatory Toxicology and Pharmacology* 80: 241-246. DOI: [10.1016/j.yrtph.2016.05.032](https://doi.org/10.1016/j.yrtph.2016.05.032).

3. Animals in drug discovery and development

3.1 Promoting the 3Rs in drug discovery and development

- Prior H, Monticello T, Boulifard V, Brennan FR, & Kimber I (2019). Integration of Consortia Recommendations for Justification of Animal Use Within Current and Future Drug Development Paradigms. *International Journal of Toxicology*. 38(4), 319–325. DOI: [10.1177/1091581819852922](https://doi.org/10.1177/1091581819852922).
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3.2 Single dose acute toxicity studies

- Chapman K, Creton S, Kupferschmidt H, Bond GR, Wilks MF, Robinson S (2010). The value of acute toxicity studies to support the clinical management of overdose and poisoning: a cross-discipline consensus. *Regulatory Toxicology and Pharmacology* 58(3): 354–359. DOI: [10.1016/j.yrtph.2010.07.003](https://doi.org/10.1016/j.yrtph.2010.07.003).
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3.3 Refining regulatory toxicology studies

- Prior H, Baldrick P, de Haan L, Downes N, Jones K, Mortimer-Cassen E, Kimber I (2018). Reviewing the utility of two species in general toxicology related to drug development. *International Journal of Toxicology* 37(2): 121-124. DOI: [10.1177/1091581818760564](https://doi.org/10.1177/1091581818760564).
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3.4 Toxicokinetics and satellite animals

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3.5 Reducing animal use in monoclonal antibody development

- Sewell F, Chapman K, Couch J, Dempster M, Heidel S, Loberg L, Maier C, Maclachlan TK, Todd M, van der Laan JW (2017). Challenges and opportunities for the future use of monoclonal antibody development: improving safety assessment and reducing animal use. *MAbs* 9(5): 742-755. DOI: [10.1080/19420862.2017.1324376](https://doi.org/10.1080/19420862.2017.1324376).
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