Survey of education and training programmes in Australia and New Zealand: current status and future prospects

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Introduction

In Australia and New Zealand, appropriate education and training of researchers, teachers, animal care staff and Animal Ethics Committee members are regulatory requirements and an integral part of institutional governance relating to the use of animals in science. However, in both countries, the relevant legislative and regulatory frameworks offer no direct guidance on required standards of education and training for people involved in the care and use of animals in research and teaching. Consequently, organisational trainers develop and provide a diverse range of education and training options for their own personnel.

At the 2016 ANZCCART (Australian & New Zealand Council for the Care of Animals in Research and Teaching) conference, the authors outlined the range of different Australian and New Zealand organisational programmes, and summarised international education and training requirements for people working with animals in research and teaching (Bourke & Lindeman 2016).

Many other countries have established minimum formal training and curriculum requirements or frameworks. Canada, United States of America (USA), United Kingdom (UK) and the European Union (EU) have structured guidelines or legal mandates governing the education and training of personnel working with animals in research and teaching. The general course content is very similar between Canada and the USA. Similarly, the EU and UK have recently harmonised their education and training. Overall, the key components of these various international education and training programmes are now well aligned in these regions.

In 2016, the authors proposed a follow-on survey to assess how individual ANZCCART members viewed the current state and future direction of education and training programs for people involved in the care and use of animals in science within Australia and New Zealand. This was strongly supported by the conference delegates.

Survey design

A survey was created using the Qualtrics survey tool. The survey was designed to be voluntary and anonymous, as this was considered important to encourage frank responses. Approval to conduct this research was provided by the University of Western Australia, in accordance with their human ethics review and approval procedures.

Survey distribution

ANZCCART was distributed the survey via email to their membership list. It was accessible for completion for a period of two weeks, from 8th -22nd August 2017. The estimated survey completion time was 10-15 minutes.

The overall aim of the survey was to seek feedback on:

- current programmes and opportunities offered by institutions;

- identified deficiencies and suggested improvements for the future; and
- future potential for standardisation of education and training in the region.

The survey requested responses from individual ANZCCART members. We sought feedback on education and training for people working with animals in research and teaching from personal experience, as participants, and their general perception of current offerings and future aspirations for education and training within their organisations. We also requested feedback from personal viewpoints on the potential value of standardisation of education and training for people working with animals in science.

As the survey was run during August and closed just immediately before the ANZCCART Conference 2017, only preliminary findings, selected from the survey, are presented.

Results

Response rate
In summary, 133 responses were received during the specified survey access period. Based on the number of individuals on the ANZCCART membership list, this represented a response rate of 28%.

Characteristics of respondents
In relation to current country of residence, 58% of respondents were resident in Australia, and the remaining 42% lived in New Zealand.

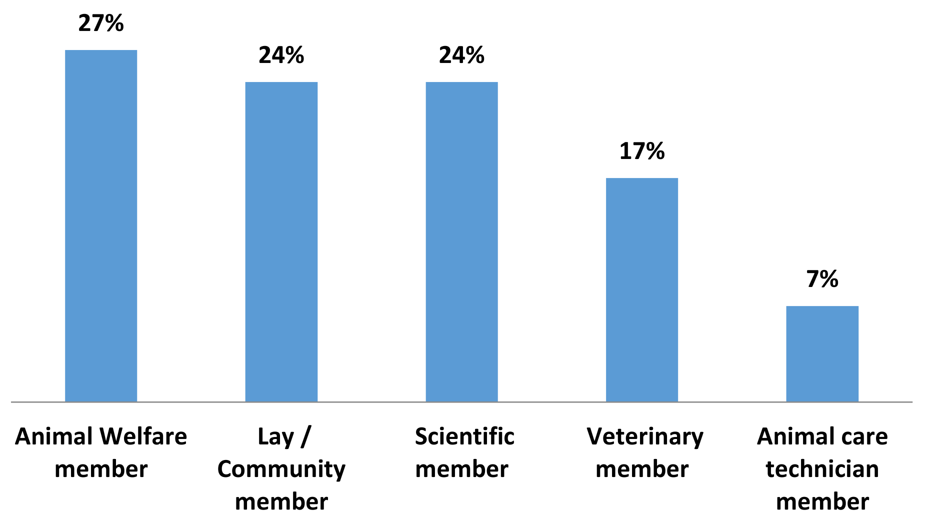
Responses were received from a broad cross-section of people involved with the use of animals in science, as indicated in Table 1.

Table 1. Profile of respondents

Category of Respondent	Percentage
Researcher Staff	23.70
Teaching Staff	8.09
Animal Care Staff	6.36
Animal Ethics Committee (AEC) member	24.28
Animal Ethics Administrator	11.56
Animal Welfare Officer	4.62
Postgraduate Student (PhD & Master)	4.05

In relation to those respondents who indicated that they participated in an Animal Ethics Committee (AEC), all categories of AEC membership were well represented as shown in Figure 1. Note: unlike the other categories of membership, the Animal care technician member is not mandatory on all AECs.

Figure 1. Category of Animal Ethics Committee membership represented



Views on current education and training programmes

The majority of respondents had attended all (73%) or part (15%) of their organisation's education and training programme. Only 12% had not attended any of their organisation's education and training.

Overall, there was no stand-out mode of delivery. Generally, most organisational training programmes comprise a combination of formats, with a relatively balanced split across delivery modes with online modules (28.02%) ; face to face theory sessions (31.32%); and practical skills training (hands on with animals) (35.71%) all utilised. In addition, some other delivery formats (4.95%), e.g. ad hoc seminars, were also used.

The mode of delivery of commonly offered topics (e.g. regulations, legislation, animal handling, pain & distress, monitoring etc.) was highly variable and across all formats.

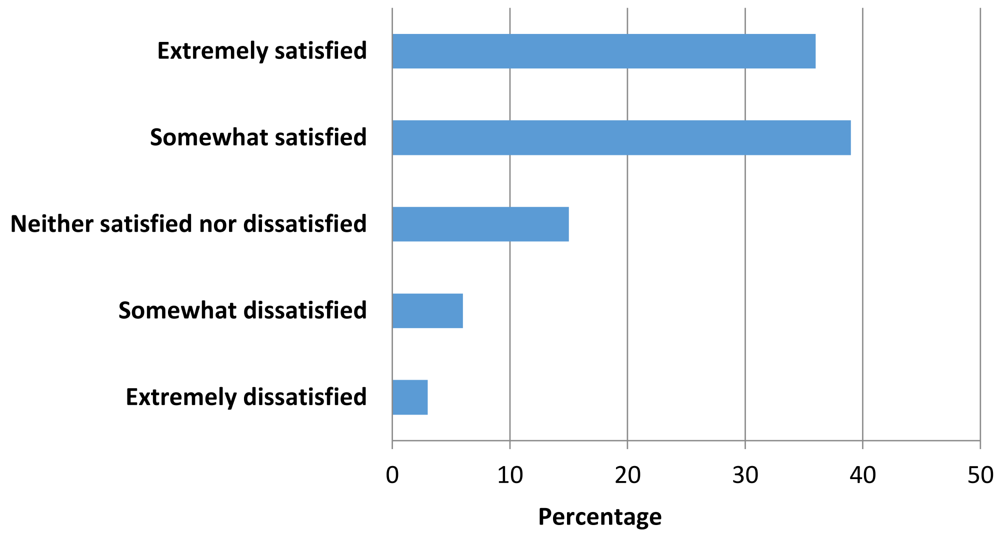
Most of the respondents (>72%) who had attended their organisational education or training programme found the content to be either 'Extremely' or 'Very' useful (Table 2).

Table 2. Usefulness of the content in programmes attended by respondents

Response rating	Programme attendees (%)
Extremely useful	36.42
Very useful	36.09
Moderately useful	16.74
Slightly useful	7.96

Overall, 36% respondents who had attended education or training were 'extremely satisfied' with the training they received and another 39% were 'somewhat satisfied'. Less than 10% were 'somewhat' or 'extremely dissatisfied (Figure 2).

Figure 2: Satisfaction with education and training received by respondents



For staff transferring between organisations, more than 40% of respondents did not feel confident accepting or recognising prior education and training related to the use of animals in science which had been acquired at other organisations in Australia and New Zealand.

Views on future education and training programs
Most respondents thought it would be useful if Australian and New Zealand Institutions introduced standardised education and training requirements for people involved in the care and use of animals in science (Table 3).

Table 3. Usefulness of standardised education

Rating	Respondents (%)
Extremely useful	45.74
Very useful	28.72
Moderately useful	14.89
Slightly useful	5.32
Not at all useful	3.19

Conclusion

Overall, survey respondents were reasonably positive about the usefulness and relevance of content currently being presented in their organisation's education and training programme but had an inherent lack of confidence in standards of programmes at other organisations. Consequently, this means that staff transferring between organisations will generally be required to go through another animal user education and training programme at the receiving organisation.

The survey also indicated that there was strong support for standardisation of education and training requirements for people working with animals in science in Australia and New Zealand. If the region was able to work toward a common framework and shared educational resources, not only would this be cost-effective and avoid the need to 'reinvent the wheel', but it would also facilitate mutual recognition of standards within the region.

In view of recent trends towards global collaborative research, it would also seem logical for Australia and New Zealand to develop more structured education and training which aligns with global standards and expectations, and enables animal research personnel moving overseas to meet international requirements.

As this presentation included only preliminary results, it is anticipated that more analysis of the survey data will further assist evaluation of current and future education and training standards for people involved in the care and use of animals in science, in both Australia and New Zealand.

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1. Bourke DA, Lindeman MJ (2016) *Let's discuss: Standardisation of training in Australia.* In G. Dandie (Ed.) Proceedings of 2016 ANZCCART Conference: Man or Mouse. (pp 56-62) Australian & New Zealand Council for the Care of Animals in Research & Teaching, Adelaide, 2017.

Dr Bourke is a veterinary graduate with more than 25 years' experience within teaching and research establishments. She has been a veterinary member of animal ethics committees in both the UK and Australia. She has also acted as a consultant for independent audits and as a panel member for External Reviews of educational and research establishments.

Before relocating to Western Australia, she worked at the Rowett Research Institute of Nutrition and Health in the UK, combining veterinary clinical and statutory compliance responsibilities as Named Veterinary Surgeon (under the Animals (Scientific Procedures) Act 1986). She also maintained an active research career, studying nutritional and reproductive physiology in a variety of large animal species. She progressed to Head of Animal Services, with overall responsibility for all veterinary and animal care services, and was subsequently appointed to the Senior Management Group of the Rowett Research Institute.

For the last 12 years she has been engaged as Animal Welfare and Veterinary Adviser to the University of Western Australia (UWA). In this role she provides veterinary expertise, advice and support to UWA's Research and Teaching Community and Animal Ethics Committee. She also organises and presents on the UWA Programme in Animal Welfare, Ethics and Welfare in Science (PAWES) course and other animal-related training workshops, and develops general educational resources.

De-extinction: the possibilities and the potential perils of bringing back extinct species through genetic engineering

Phil Seddon[1]
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De-extinction, the prospect of using new genetic tools to resurrect lost species, burst upon the public and scientific consciousness only in 2013, and since that time has prompted vigorous debate, a flurry of publications, but no actual species' restorations to date. The mere prospect of de-extinction is polarising, creating strong advocates and implacable opponents, with both camps invoking moral, ethical, economic, and ecological arguments for their position. Two fundamental questions arise: 1) is it really possible to resurrect an extinct species? And if so, 2) just because you can do something, doesn't mean you should – so, is de-extinction a good idea?

Detailed in the publications listed below and available for free down-load, I have explored the pros and cons of de-extinction for conservation benefit, where a justifiable rationale for attempting to resurrect extinct species is to restore lost ecosystem functions and thereby enhance the stability and resilience of natural systems. I have reached a number of conclusions:

- None of the current pathways for de-extinction, i.e. back breeding, genomic engineering, or even inter-species cloning, is guaranteed to bring back exactly what has been lost, thus in many ways, extinction still is forever and our efforts to prevent biodiversity losses must be sustained;
- Unless, and possibly even if, new resources are applied to de-extinction efforts for conservation, there is a danger of a net loss of biodiversity since de-extinction represents an opportunity cost whereby fewer resources might end up being applied to saving threatened extant species;
- De-extinction invokes a moral hazard by potentially undermining the conservation message of the finality of extinction, and this risks turning the public off the urgency of the current extinction crisis;
- So-called de-extinction technology might be best applied to the most recent species extinction, where much is known about species biology, the role in the ecosystem, and where there is greater confidence that suitable areas of habitat remain;
- Potentially great gains could be achieved by applying de-extinction technology to species that have not yet gone extinct, through the restoration of functionally extinct species via cloning, or genetic rescue of critically endangered species by re-engineering lost genetic diversity.

Potential new tools for conservation should be received gratefully, but should also be examined carefully to ensure that the proposed benefits can indeed be achieved and that any costs can be avoided or reduced. We need to take care that de-extinction does not lead to re-extinction, or worse, to new extinctions if released resurrected forms have unanticipated and undesirable impacts on their recipient systems. The pace of technological change is staggering and the next 10 years will be an exciting and invigorating time for biodiversity conservation. But as appealing as the prospect of seeing a woolly mammoth or a moa might be, I believe one of greatest contributions to be made by de-extinction will be in helping prevent species extinctions in the first place.

For a more detailed treatment of these ideas please see these freely downloadable publications:

Seddon PJ (2017) De-extinction and barriers to the application of new conservation tools. *Recreating the Wild: De-extinction, Technology, and the Ethics of Conservation*, special report, *Hastings Center Report*, no 4: S5-S8 http://onlinelibrary.wiley.com/doi/10.1002/hast.745/abstract

IUCN (2016) *IUCN SSC Guiding Principles on Creating Proxies of Extinct Species for Conservation Benefit*. Version 1.0 18 May 2016. Gland, Switzerland: IUCN Species Survival Commission. https://portals.iucn.org/library/node/46248

Phil Seddon is a Professor of Zoology and Director of the Post-Graduate Wildlife Management Programme at the University of Otago. His research interests relate to the field of Reintroduction Biology and the restoration of populations of threatened species. Phil is a member of the World Conservation Union's (IUCN) Species Survival Commission, and chaired the international IUCN Task Force that produced the 2016 Guiding Principles on De-extinction. Phil has worked in South Africa and Saudi Arabia, and now contributes to and advises on species restoration projects in New Zealand, Australia, Indonesia, Austria, Mongolia, the Middle East and North America.

The Cacophony Project: Using digital technologies to make trapping 80,000 times more efficient

Grant Ryan [1], Cameron Ryan-Pears [1]
[1]The Cacophony Project, https://cacophony.org.nz

The modern information technology used by the Cacophony Project can theoretically make eradication of predators in New Zealand 80,000 times more efficient, with a combination of sound and visual lures, artificial intelligence (AI) predator identification, and solar power.

- The lure can last 20 times longer than food traps, being solar powered.
- It potentially only requires 1/100th the number of traditional traps, because they can operate over 10 times the distance (100 times the area).
- One trap can target any predator (possum, rat, mustelid or feral cat), so only a quarter the number of traps are required.
- The kill percentage could be closer to 100%, rather than less than 10% for current traps.
- Moore's Law implies that there is likely to be a consistent exponential drop in cost and improvement in performance over time.

The Cacophony Project is totally open source, so any time there are improvements made they can be rolled out to all the networked traps. These collective improvements mean that, theoretically, the traps could be 80,000 times more efficient: 20 (lure life) x 100 (trap intensity) x 4 (one trap, four pests) x 10 (kill ratio). This project has been going for 2 years, and has succeeded in:

- creating a device to turn any old smartphone into an objective environmental monitoring tool;
- encouraging initial testing of digital lures that shows possums can be detected and lured from a distance;
- using artificial intelligence (AI) to automatically identify different predators from video analysis;
- achieving a way to robustly measure the effectiveness of existing traps and monitoring tools (existing traps work as little as 1% of the time);
- developing a super-sensitive dual camera tool (heat and infrared) to monitor predators better than any existing tool, which should be particularly useful for other scientific projects but will ultimately form the core of the automated trap.

For more details and references see https://cacophony.org.nz/blog

Grant is an addicted inventor who is now using information technologies to make NZ predator free. He has started numerous high tech companies - GlobalBrain (sold to NBCI), RealContacts (sold to Intel), Eurekster, SLI-Systems (listed on NZX), YikeBike and PurePods. He has a degree in Mechanical Engineering and PhD in Ecological Economics.

Moore's Law – twice as good or half the price every 18 months

Open source – collective intelligence

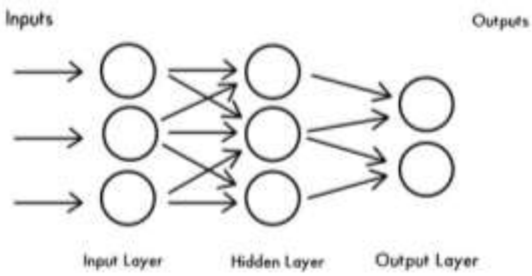
Optimal camera for predator control

www.cacophony.org.nz

Video tool optimised for New Zealand predators

Predator recognition 100%

Artificial Intelligence - machine learning...



Device effectiveness

Complete guess						
Some data						
[illegible]						

Animal traps	Possum	Rat	Stoat	Rabbit	Hedgehog	Mouse
Good Nature	[illegible]	< 15%	< 10%			
Timms (or other head-in-hole, over-centre-trigger traps, e.g. Trapinator	[illegible]	[illegible]				
Leg hold	[illegible]					
Doc 200		[illegible]	[illegible]			[illegible]
Poison station	?	?	?	?	?	?
Live capture	30%	?			80%	
Spitfire	10%	<30%	55%			

Animal tracking tools	Possum	Rat	Stoat	Rabbit	Hedgehog	Mouse
Tracking tunnel		<90%	55%			
Motion sensor cameras	95%	95%	75%			
Chew cards	50%	50%	10%			
Real time motion camera	100%?	100%?	100%?			

www.cacophony.org.nz

Digital lures – social sounds

Cover much larger area

Species specific

Longer lasting (not eaten by non targets)

Even more effective in reinvasion or low numbers

May only need to attract and kill half population (males/females)

Evolve faster than predators

Digital lures summary

P = Theoretically possible,
E = some evidence it works (literature and or our testing)
V = [illegible]

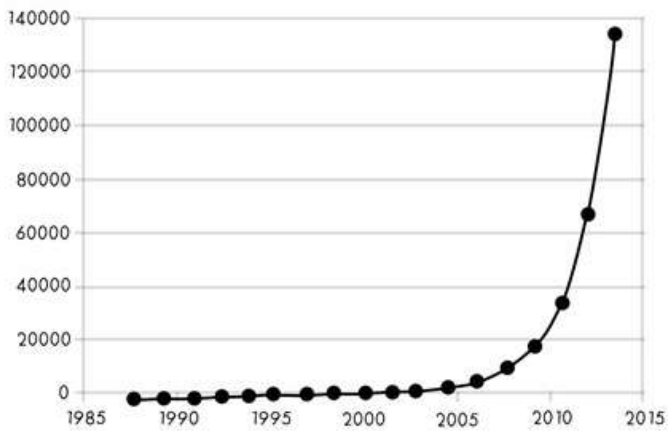
	Possum	Rat	Stoat	Rabbit	Cat
Listen to hear if they are out there	P	P	P		
Sound call to get a response to confirm if they are there.	V				
Digital sound to draw into the trap area (caught on video)	E	P	P		E
Digital image to draw into trap area (video records them)	E			E	
Sound/image to hold the pest for long enough for AI identification	E				
Sound/image hold the pest in area enough for a identification and kill	P				
Sound that can be used as a deterent	V				

www.cacophony.org.nz

List of project for next phase

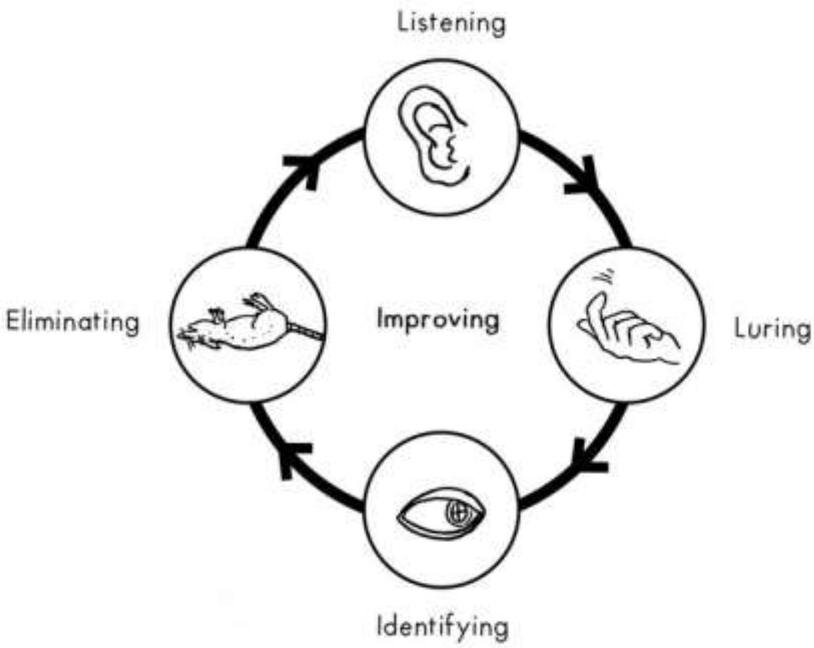
- Device that can monitor 100% of predators with AI
- Get real data for effectiveness of existing traps and monitoring
- Rapidly test lots of digital lures (sound and light)
- Identify at a distance predators in area
- 100% kill method – paint ball, spay, aerosol, infrasound, poison dart

Moore's Law - Impossible becomes normal



Open Source is a beautiful thing

Menno Finlay-Smits – Project Manager/serior developer
Cameron Ryan-Pears – hardware/software engineer for project
Dave Lane - Open source design and Drupal CMS integration
Tim Hunt - Ap development
Jessica Lyons - Social media
Brent Martin - Machine learning (University of Canterbury)
Elaine Murphy (DOC/Lincoln) - animal behaviour
Tim Sjoberg (ZIP) - animal behaviour
Matt Kavermann - Digital lures
Michael Busby - Website design and development
Max Johns - Content
Gray Rathgen - Designer



Ethical considerations

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What is humane.....?

100% eradication for an area never need do it again

Safest poison delivery system

Lower leg hit only

Need to lick off

Lower dose than for human

Currently safe enough for helicopter drop...

Cam Reid Oration - New 3Rs techniques

Helena Hogberg
The Johns Hopkins University, Bloomberg School of Public Health, Center for Alternatives to Animal Testing, Baltimore, Maryland, USA

The principles known as the "3Rs" of animal testing alternatives were defined by Russell and Burch (Russell & Burch 1959) and comprise *Replacement, Reduction,* and *Refinement.* Replace: don't use animals if a non-animal method exists that can answer the scientific question at hand. Reduce: if you must use animals, keep the number to the minimum necessary to answer the question. Refine: if you must use animals, keep any pain or distress they experience to a minimum.

For over 35 years, the Center for Alternatives to Animal Testing (CAAT) has been a leading force in the promotion of the 3Rs and humane science by supporting the creation, development, validation, and use of alternatives to animals in research, product safety testing, and education. CAAT's main focus has been toxicology, as this was identified as a field where changes could be implemented most rapidly (Hartung 2017). There are several validated and accepted alternative methods to animal tests that are used in regulatory toxicology (OECD 2005). These methods have been recognised by regulators, including OECD, FDA, and EPA, as valuable tools of modern toxicology (Kandarova & Letasiova 2011). Over the last decades there have been new regulations, (such as the Registration, Evaluation, Authorisation, and Restriction of Chemicals (REACH) in EU and the Toxic Substances Control Act (TSCA) reauthorisation in US, for chemicals already registered and marketed that require additional toxicology data. The generation of new data for REACH has unfortunately led to tremendous costs and numbers of animals used (Hartung & Rovida 2009). Despite the existence of many validated *in vitro* tests, they are rarely used (Rovida *et al.* 2011).

The main alternative method used for registration of additional data has been *read-across*, a computational tool that makes use of already available data on information-rich chemicals to predict the properties of data-poor chemicals with similar chemical structures (Maertens *et al.* 2016). Problematically, expertise in *read-across* is rare both in industry and regulators, with the consequent low acceptance of these data by agencies (e.g., European Chemicals Agency (ECHA)). Therefore, CAAT and collaborators created an initiative to facilitate read-across that included several workshops and stakeholder forums (Patlewicz *et al.* 2014). Two main publications were generated with the aim of clarifying and guiding read-across users in "Good Read-across Practice" (Ball *et al.* 2016; Zhu *et al.* 2016). In parallel, ECHA has published a Read Across Assessment Framework (RAAF), demonstrating how to present read-across data to regulators through robust scientific justification (ECHA 2015). Read-across has the opportunity to reduce and replace animal testing for toxicological assessment, especially with the availability of large quantities of public data and test results acquired for chemicals with well-characterised structures and physical properties. The largest collection of chemical toxicity data currently is the REACH database, which was made machine-readable by Luechtefeld et. al. (2016) to demonstrate the extent and diversity of the dataset and how an open-access REACH programme could facilitate a profound change in computational toxicology (Luechtefeld *et al.* 2016a,b,c,d). This work also generated a commercially available software application in collaboration with Underwriters Laboratories (UL), REACH*Across*™ (https://www.ulreachacross.com), which builds large networks of chemicals based on molecular structure and health-endpoint interactions. Not only do these computational tools help to correlate toxicity data of chemicals, they can also provide information on reproducibility of tests. Surprisingly, many chemicals have been subjected to the same test multiple times—for example, using these computational tools for the REACH database showed that two substances were repeatedly tested in TG 405 (Draize eye test) more than 90 times, and 69 chemicals were repeatedly tested more than 45 times (Luechtefeld *et al.* 2016a). This is a tremendous waste of animals that could be avoided if data were easily readable and publically accessible.

Most stakeholders agree that it is time for a paradigm shift in toxicology. The National Research Council report from 2007, *Toxicity Testing in the 21st Century: A Vision and a Strategy* (Tox-21c), has led this transition in the US (NRC 2007). It suggests moving away from traditional (animal) testing to modern technologies based on toxicity pathways. Today, companies and agencies still largely use animal studies to assess toxicological risks, although they are costly (about $1 billion a year in the US) and too slow to provide answers to the complex toxicological questions posed. This has led to the current lack of toxicological information required to safeguard human health and guide regulatory decision-making on chemicals. In addition, the animal studies are not necessarily relevant to humans. In fact, it is known that 90-97% of substances fail in clinical trials due to lack of efficiency or side-effects in humans that were not identified in preclinical animal tests (FDA 2004). Moreover, the hazard assessment is based on an extrapolation where the animal is exposed to a high dose that is not at all relevant to human scenarios (which is often characterised by low-dose, long-term exposure). The Tox-21c approach has therefore been well received by regulatory agencies, even though it still needs to be fully applied in practice. The most recent adaptation by the US Environmental Protection Agency (EPA) for their toxicity testing strategy, in particular, has initiated a debate about how to create a novel approach based on human cell cultures, lower species, high-throughput testing, and modelling (Hartung 2009). One of the challenges has been to convince regulators that the concept of toxicity pathways can be linked to an adverse effect (as per the definition: "Cellular response pathways that, when sufficiently perturbed, are expected to result in adverse health effects") (NRC 2007). To tackle this challenge, current OECD developments aim to organise our knowledge on hazard manifestations as Adverse Outcome Pathways (AOP), which includes all steps, including chemical properties of the toxicant, molecular initiating event, cellular responses, organ responses, organism responses and population responses (http://www.oecd.org/chemicalsafety/testing/adverse-outcome-pathways-molecular-screening-and-toxicogenomics.htm). The concept of toxicity pathways is part of AOP and describes the molecular definition of mechanism and the perturbed networks (molecular initiating event, cellular responses, and organ responses).

Even though our basic *in vitro* cell models have been very useful for mechanistic studies, it has become evident that more complex models, such as three dimensional (3D) test systems and organotypic cell cultures, are essential in reproducing the architecture and function of an organ. Many reports indicate that the third dimension in cell cultures is important for improvement of drug discovery and toxicity testing, as these models are much closer to *in vivo* compared to two-dimensional cultures (Abbott 2003; Gassmann *et al*. 2012; Hartung 2014). One of the substantial investments into new tools is the development of human-on-a-chip approaches, which may bring about a second generation of alternatives. One example is the collaboration between NIH (NCATS), the Defense Advanced Research Projects Agency (DARPA), and FDA focused on research projects designed to create 3D cell models of 10 human organ systems (NIH 2012). The aim is to later combine the different organ models on a transparent microchip to create a human-on-a-chip for toxicity testing.

Our own research group was funded by the NIH within this programme to develop a 3D brain model from human induced pluripotent stem (iPSCs). The model consists of several different cell types, such as neurons, astrocytes, and oligodendrocytes that reproduce neuronal-glial interactions and connectivity (Hogberg *et al.* 2013; Pamies *et al.* 2014; Pamies *et al.* 2017). In addition, it has shown critical elements of neuronal function—synaptogenesis and neuron-to-neuron (e.g., spontaneous electric field potentials) and neuronal-glial function (e.g. myelination)—that mimic the microenvironment of the central nervous system (rarely seen *in vitro*). The model has been used for numerous different applications, including (developmental) neurotoxicity (Pamies *et al.* 2017), Parkinson's disease, cancer, resilience, blood-brain barrier, autism, Down syndrome, inflammation, Zika, and other viral infections (additional manuscripts in preparation). The possibility of infecting this human iPSCs model with viruses such as Zika and JC-virus is especially exciting, as very few animal and *in vitro* cell models have been able to recapitulate these pathologies.

In summary, animal models do not necessarily predict human effects and diseases, which is why they should not be considered the "golden" standard. This has been widely acknowledged and most stakeholders recognise that there is a need for a paradigm shift in how we assess toxicology. There are several novel tools, such as *read-across*, 3D cell models, iPSCs and human-on-a-chip approaches that will become useful for the reduction, and replacement, of animal testing.

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What are the 3Rs?

REPLACEMENT: Don't use animals if a non-animal method exists that can answer the scientific question at hand.

REDUCTION: If you must use animals, keep the number to the minimum necessary to answer the question.

REFINEMENT: If you must use animals, keep any pain or distress they experience to a minimum.

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Read-across

Chemical Toxicity Prediction
Category Formation and Read-Across

Data-rich substances registered 2010 and 2013:

75% of dossiers use read-across

Other alternatives hardly used

Expertise in industry low

Low acceptance by ECHA

Read-across
Data gap filling concluding from (structurally) similar chemicals

Category approach
Test only representatives of a group of similar chemicals or complex mixtures


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Read-across
ALTEX 2016
33, 149-166
transatlantic think tank for toxicology
t4 report*
Toward Good Read-Across Practice (GRAP) Guidance
Nicholas Ball[1§*], Mark T. D. Cronin[2*], Jie Shen[3*], Karen Blackburn[4], Ewan D. Booth[5], Mounir Bouhifd[6], Elizabeth Donley[7], Laura Egnash[7], Charles Hastings[8], Daland R. Juberg[1], Andre Kleensang[6], Nicole Kleinstreuer[9], E. Dinant Kroese[10], Adam C. Lee[11], Thomas Luechtefeld[6], Alexandra Maertens[6], Sue Marty[1], Jorge M. Naciff[4], Jessica Palmer[7], David Pamies[6], Mike Penman[12], Andrea-Nicole Richarz[2], Daniel P. Russo[13], Sharon B. Stuard[4], Grace Patlewicz[14], Bennard van Ravenzwaay[10], Shengde Wu[4], Hao Zhu[13] and Thomas Hartung[6,15]
The Read-Across Assessment Framework (RAAF)
March 2017
ECHA
EUROPEAN CHEMICALS AGENCY
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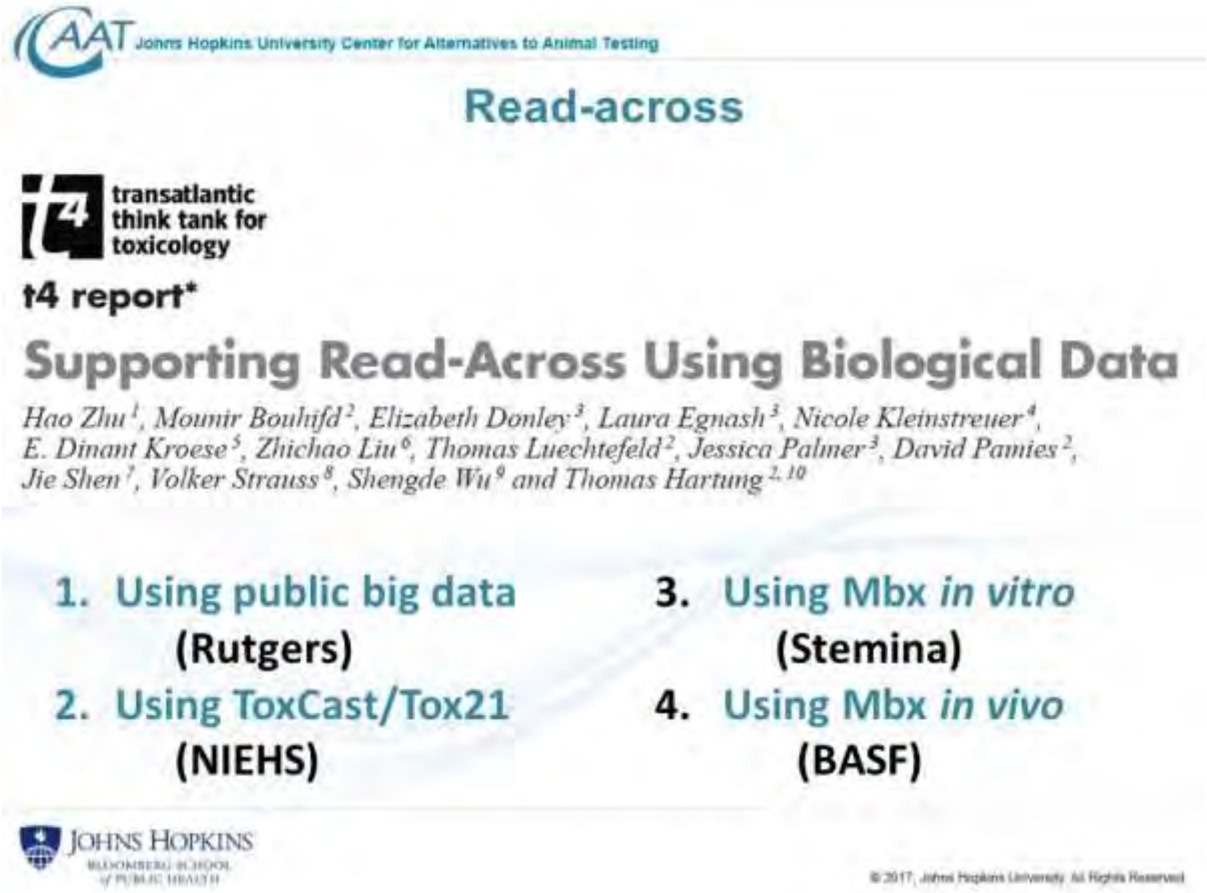
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Read-across
transatlantic think tank for toxicology
t4 report*
Supporting Read-Across Using Biological Data
Hao Zhu[1], Mounir Bouhifd[2], Elizabeth Donley[3], Laura Egnash[3], Nicole Kleinstreuer[4], E. Dinant Kroese[5], Zhichao Liu[6], Thomas Luechtefeld[2], Jessica Palmer[3], David Pamies[2], Jie Shen[7], Volker Strauss[8], Shengde Wu[9] and Thomas Hartung[2,10]
1. Using public big data (Rutgers)
2. Using ToxCast/Tox21 (NIEHS)
3. Using Mbx in vitro (Stemina)
4. Using Mbx in vivo (BASF)
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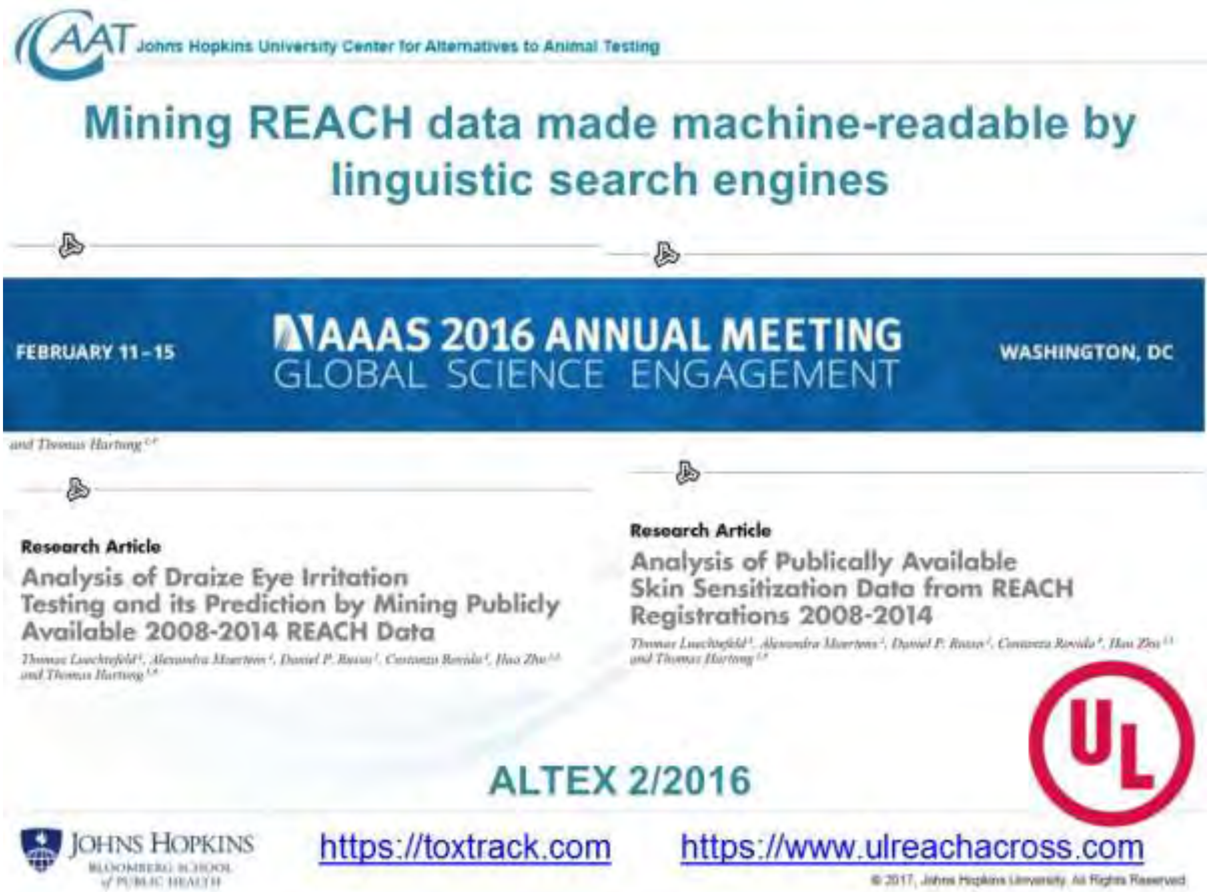
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Mining REACH data made machine-readable by linguistic search engines
FEBRUARY 11–15
AAAS 2016 ANNUAL MEETING
GLOBAL SCIENCE ENGAGEMENT
WASHINGTON, DC
Research Article
Analysis of Draize Eye Irritation Testing and its Prediction by Mining Publicly Available 2008-2014 REACH Data
Research Article
Analysis of Publically Available Skin Sensitization Data from REACH Registrations 2008-2014
ALTEX 2/2016
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https://toxtrack.com
https://www.ulreachacross.com
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nature
Legal tussle delays launch of huge toxicity database
Science, 12 Feb 2016
TOXICOLOGY
A crystal ball for chemical safety
By comparing new chemicals to known compounds, toxicologists seek early hazard warnings
Troubling resemblances
Nature online and Scientific American
Legal Tussle Delays Launch of Huge Toxicity Database

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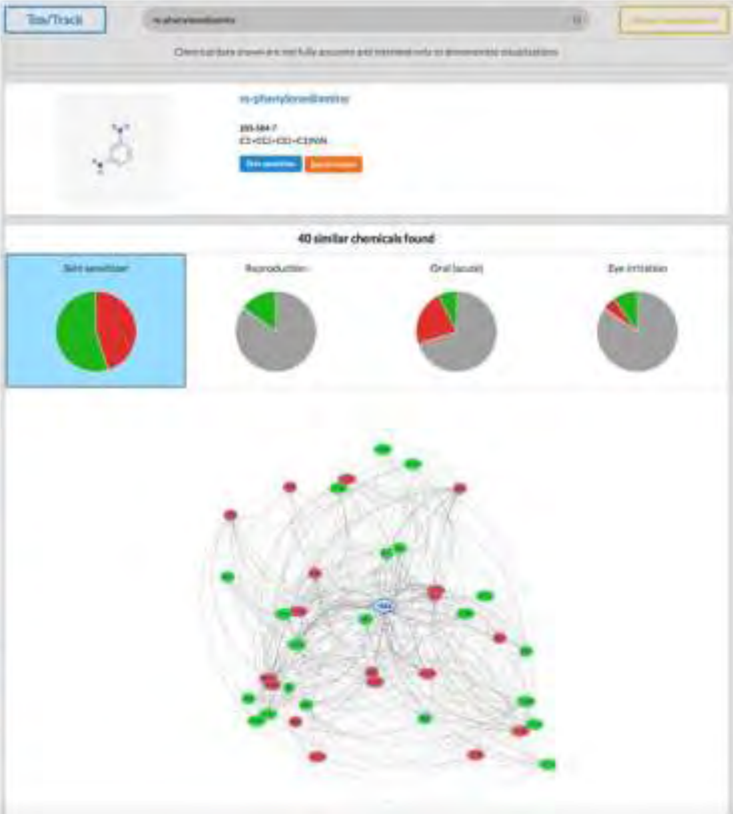

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Repetitions of Guideline 405: Acute Eye Irritation/Corrosion

Repeats	Number substances	Example ECNumber
90	2	613-683-0,295-445-2
45	69	940-595-2,295-431-6
18	1	931-203-0
15	2	700-762-0,692-840-5
13	38	934-268-3,931-515-7
12	2	918-317-6,500-513-4
11	2	931-700-2,226-109-5
10	2	232-395-2,939-581-9
9	1	267-291-6
8	27	940-730-5,940-728-4
7	32	940-727-9,940-726-3
6	75	931-745-8,300-226-2
5	56	939-578-2,939-575-6
4	135	939-693-8,939-621-5
3	254	939-715-6,939-688-0
2	593	208-778-5,941-224-7
1	2388	293-029-5,273-224-1

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Toxicology in the 21st Century

Johns Hopkins Bloomberg School of Public Health

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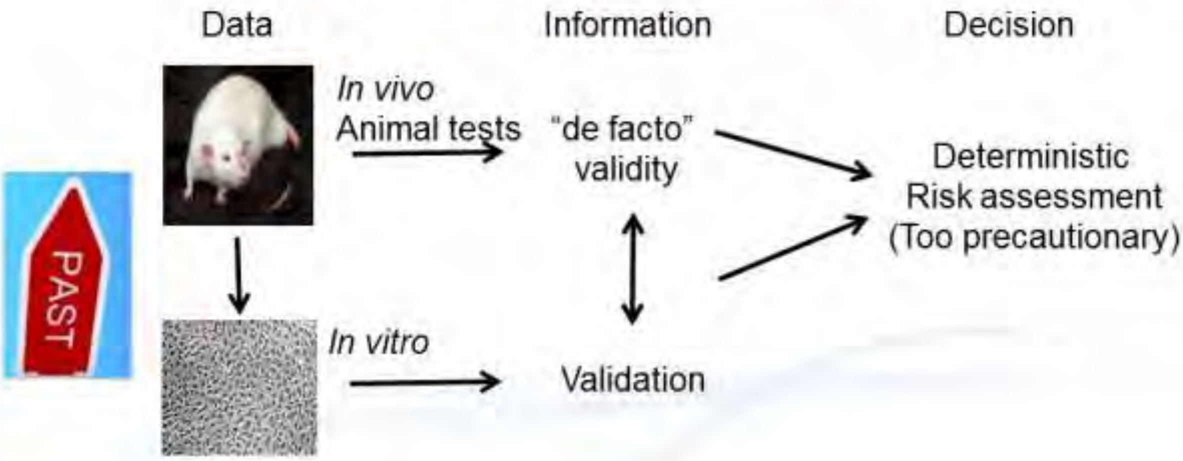
Paradigm shift in toxicology



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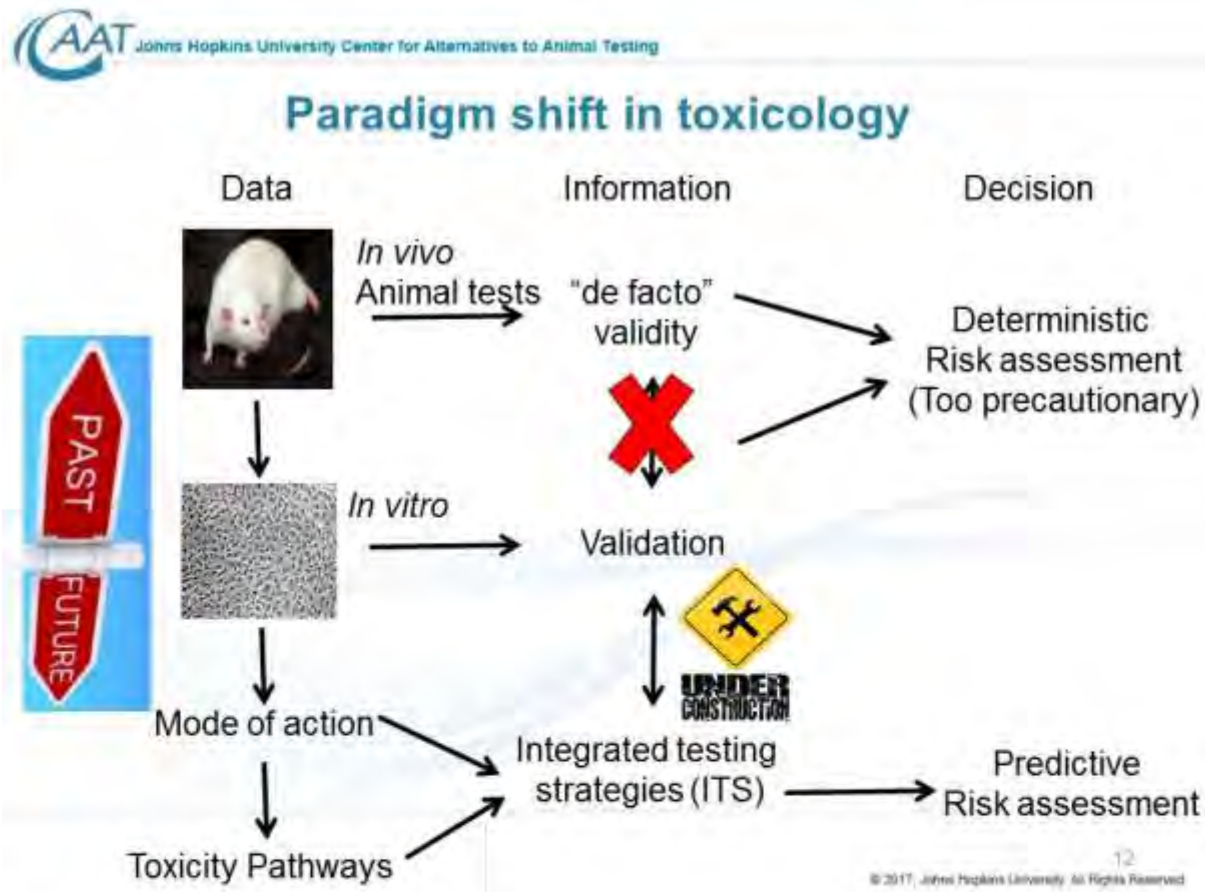

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Concerns regarding the relevance to human health effects

- 85-92% of substances fail during clinical trials due to effects in humans that were not identified in preclinical animal tests *(FDA, 2004)*.
- High-dose to low-dose extrapolation. Testing can be performed only at high doses not relevant for human exposure scenarios.
- Difficult to test mixtures, we are not exposed to one compound at a time.
- Inter individual/species differences is not reflected in the animal tests.

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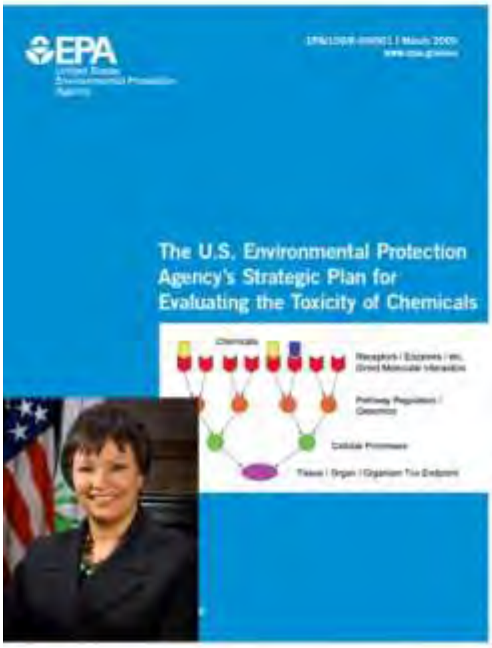
NAS vision report Tox-21c



"With an advanced field of regulatory science, new tools, including functional genomics, proteomics, metabolomics, high-throughput screening, and systems biology, we can replace current toxicology assays with tests that incorporate the mechanistic underpinnings of disease and of underlying toxic side effects."
M.A. Hamburg, FDA 2011

"We propose a shift from primarily in vivo animal studies to in vitro assays, in vivo assays with lower organisms, and computational modeling for toxicity assessments"
F. Collins, NIH, 2008

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The Frank R. Lautenberg Chemical Safety Act = TSCA reauthorization

(The Toxic Substance Control Act)

22 June 2016

REACH, Korea-REACH, Taiwan-REACH, Canadian Environmental Protection Act, 1999 (CEPA 1999) , discussions in China, ...

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"The Administrator shall reduce and replace, to the extent practicable, scientifically justified, and consistent with the policies of this title, the use of vertebrate animals in the testing of chemical substances or mixtures"

- available existing information, including (i) toxicity information; (ii) **computational toxicology** and bioinformatics; and (iii) **high-throughput screening** methods and the prediction models of those methods;
- encouraging and facilitating — (i) the use of scientifically **valid test methods and strategies** that reduce or replace the use of vertebrate animals while providing information of equivalent or better scientific quality and relevance that will support regulatory decisions…, (ii) the **grouping** of 2 or more chemical substances into scientifically appropriate categories … (iii) the formation of industry **consortia**

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- Within 2 years **strategic plan** to promote the development and implementation of alternative test methods and strategies…, for example— (i) computational toxicology and bioinformatics; (ii) high-throughput screening methods; (iii) testing of categories of chemical substances; (iv) tiered testing methods; (v) in vitro studies; (vi) systems biology; (vii) new or revised methods identified by validation bodies [ICCVAM, OECD] ; or (viii) industry consortia
- a **list**, …update on a regular basis, **of particular alternative test methods or strategies**, …public notice and comment
- **Every 5 years submit to Congress a report** that describes the progress made in implementing the plan … and goals for future alternative test methods and strategies implementation;
- prioritize and … **carry out performance assessment, validation, and translational studies** to accelerate the development of test methods and strategies that reduce, refine, or replace the use of vertebrate animals, including minimizing duplication

Alternative Methods have arrived in US legislation

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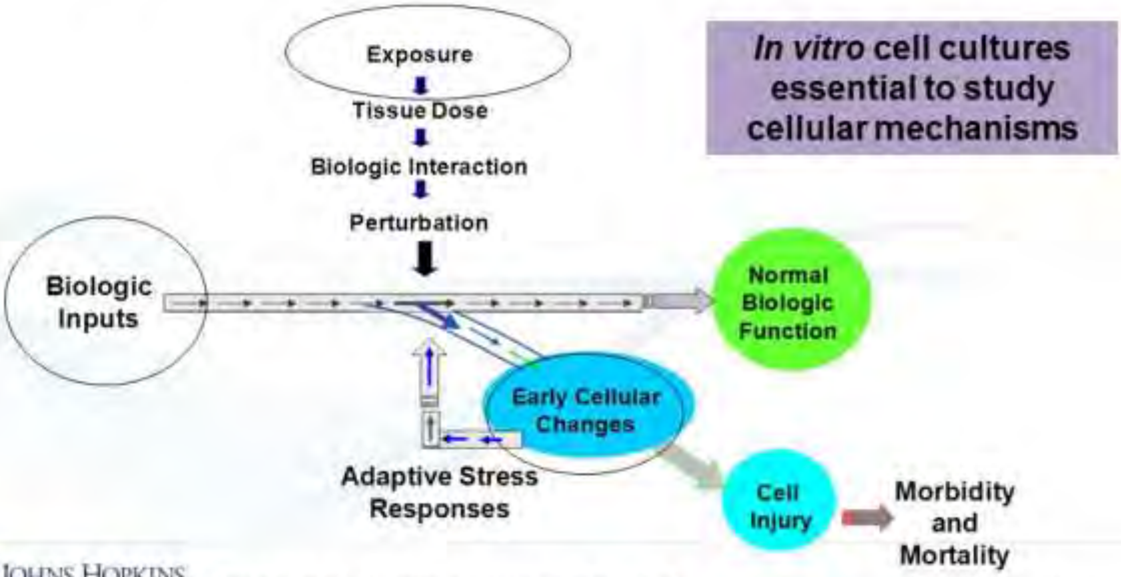
Toxicity pathways

Definition: Cellular response pathways that, when sufficiently perturbed, are expected to result in adverse health effects *(NRC 2007)*.



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NRC 2007 | National Research Council: Toxicity testing in the 21st century a vision and a strategy. 1st ed. ed

18

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OECD

ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT

PROPOSAL FOR A TEMPLATE, AND GUIDANCE ON DEVELOPING AND ASSESSING THE COMPLETENESS OF ADVERSE OUTCOME PATHWAYS

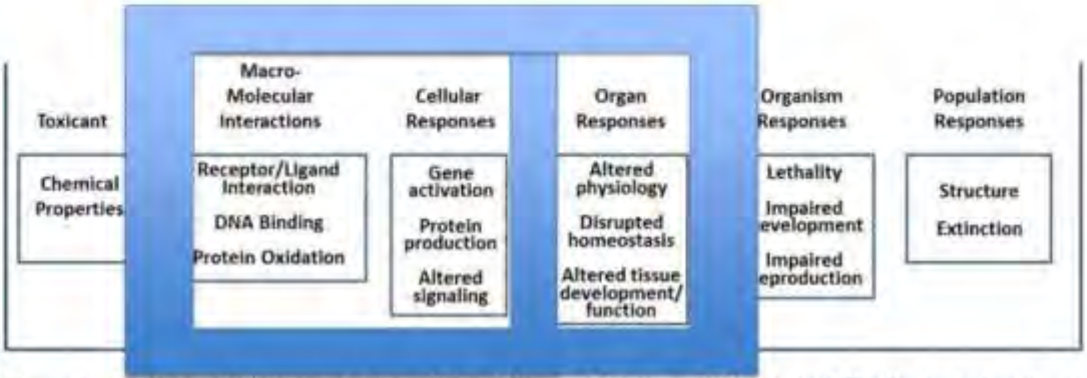

Figure1. A schematic representation of the Adverse Outcome Pathway (AOP) illustrated with reference to a number of pathways.

Toxicity Pathways

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Human-on-chip

- Started as a program for countermeasures to bioterrorism
- Multi millionaire programs
  - DARPA (Defense Advanced Research Agency), NIH and FDA
  - DTRA (Defense Advanced Research Agency)
  - EU project (Body-on-chip)

For more information:
http://www.ncats.nih.gov/tissuechip

http://www.extremetech.com/extreme/167748-us-army-develops-human-on-a-chip-tech-for-chemical-testing-fleshy-robot-soldiers

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http://en.wikipedia.org/wiki/Organ-on-a-chip

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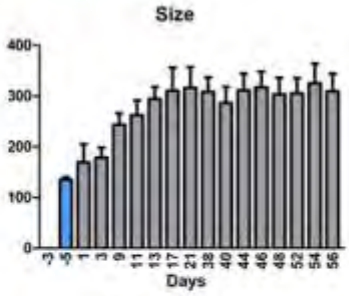
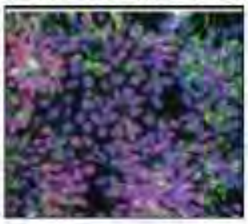
Human iPSC-derived 3D neural model



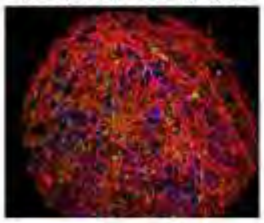
iPSCs

Neural Precursor Cells



Gyratory Shaking

3D brain culture



Hogberg et al., (2013) Stem Cell Res Ther. 4(Suppl 1:S4)
Pamies et al., (2014), Exp Biol Med 239:1096-107
Pamies et al., (2017), Altex 34(3):362-376

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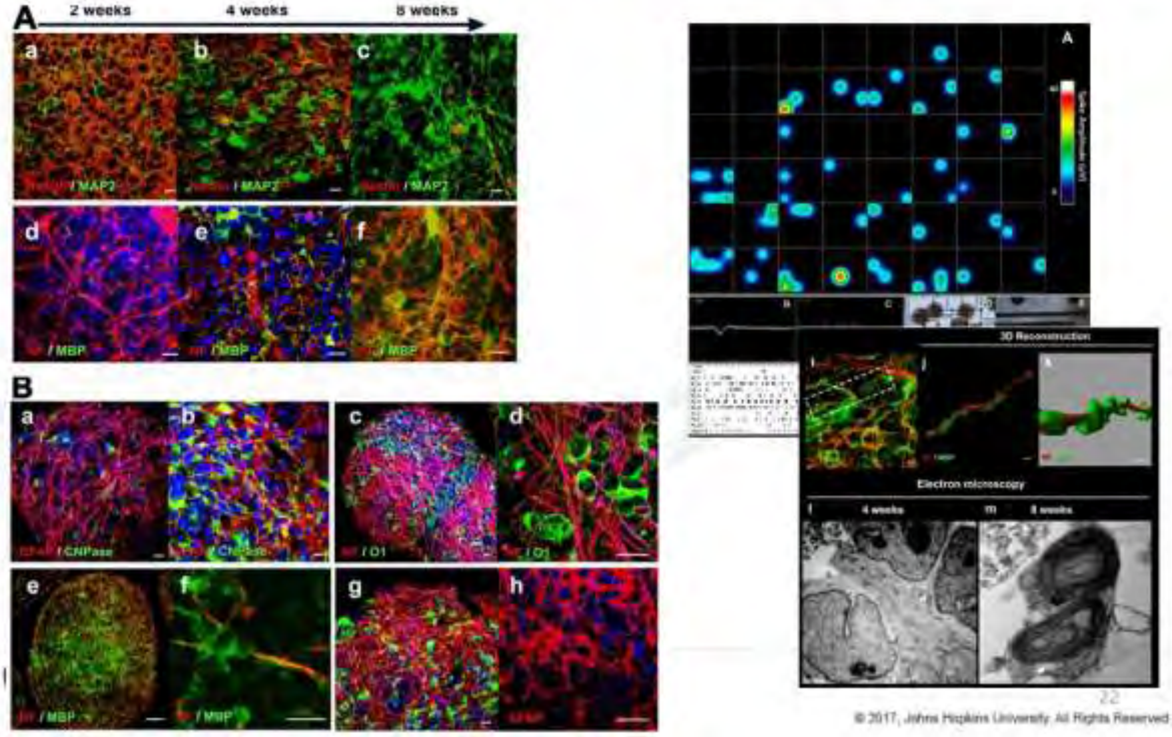
Poster:

iPSC-derived human mini-brains



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Applications

- (Developmental) Neurotoxicity
- Parkinson's disease
- Dys- and de-myelination
- Cancer
- Resilience
- Blood-Brain Barrier
- Autism
- Down's Syndrome
- Inflammation
- Zika and other virus infections

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Zika virus

- Zika is spread mostly by the bite of an infected mosquito.
- Zika infections during pregnancy can lead to microcephaly and other severe brain defects.
- Infected adults can get Guillain-Barré or other neurological conditions.
- Few animal models have been able to be infected by zika.

John Cunningham (JC) Virus

- More than 50% of people have been infected.
- Virus lies dormant in the central nervous system inactive but can be reactivated in immune suppressed people and lead to severe brain infections.
- No animal or *in vitro* model have been able to be infected by JC virus.

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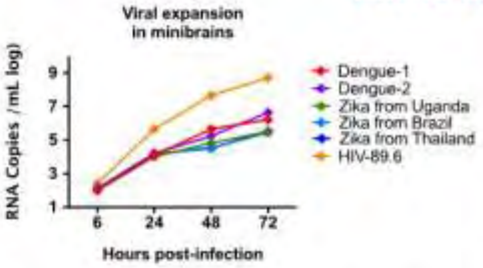
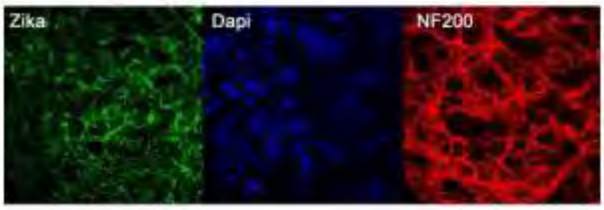
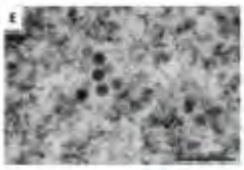
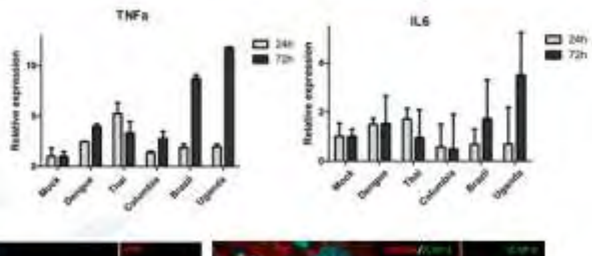
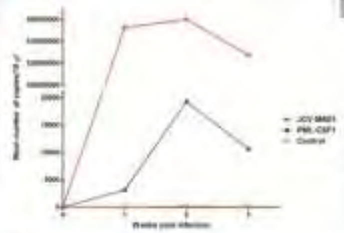
Zika and JC Virus

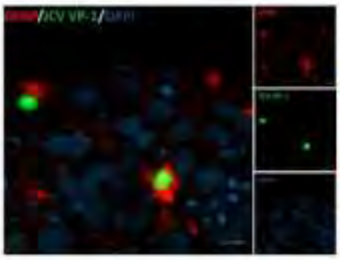


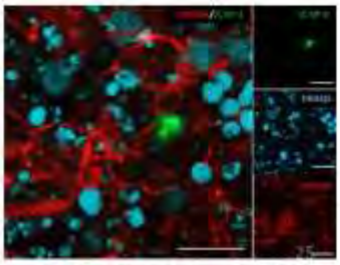












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Summary

- Animal models do not necessary predict human effects and diseases why they should not be the "golden" standard.
- Regulatory and governmental recognition of the a paradigm shift in toxicology.
- Read-across useful tools for replacing animal testing.
- Human iPSCs models can be used to understand genetic disorders and gene and environmental interactions.
- Human 3D models can be infected by some viruses not able to infect animals.
- Alternative approaches have the potential to reduce and replace the use of animal models.

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"All models are wrong, but some are useful" (George E.P. Box)

https://www.youtube.com/watch?v=52lL9gemyDw

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27

From glowing grubs to superbugs: the 3Rs and infectious diseases research

Siouxsie Wiles
Molecular Medicine and Pathology, University of Auckland, New Zealand

Bioluminescence (literally ‘living light’) has evolved in a wide variety of fascinating organisms with many different purposes. It allows glow worms and anglerfish to lure food, fireflies to find a mate and nocturnal squids to camouflage themselves from predators. The light is produced as a by-product of an enzyme (‘luciferase’) reaction, emitted when a substrate (‘lucferin’) is exposed to oxygen. This talk highlights Siouxsie’s research using bioluminescence to better understand infectious diseases, from tracking infections in living animals to discovering new antibiotics.

Dr Siouxsie Wiles is an award-winning scientist who has made a career of manipulating microbes. She and her team at the University of Auckland engineer bacteria to glow to understand how superbugs make us sick and to find new medicines. Siouxsie studied medical microbiology at the University of Edinburgh, followed by a PhD in microbiology at the Centre for Ecology and Hydrology in Oxford. She spent almost a decade working at Imperial College London, before relocating to New Zealand as a Health Research Council Hercus Fellow in 2009. Siouxsie’s commitment to the ethical use of animals in research saw her awarded the inaugural UK National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs) prize in 2005 and the New Zealand National Animal Ethics Advisory Committee (NAEAC) 3Rs prize in 2011. In 2016, Siouxsie was named a Blake Leader by the Sir Peter Blake Leadership Trust. She recently published her first book, ‘Antibiotic resistance: the end of modern medicine?’, as part of the BWB Texts series.

From glowing grubs to superbugs: the 3Rs and infectious diseases

Dr Siouxsie Wiles

University of Auckland

@SiouxsieW

Part I

The micropocalypse!

@SiouxsieW

https://vimeo.com/180908160

@baym

"the end of modern medicine as we know it"

Margaret Chan, Director General

World Health Organisation

Part II

Glowing grubs...

@SiouxsieW

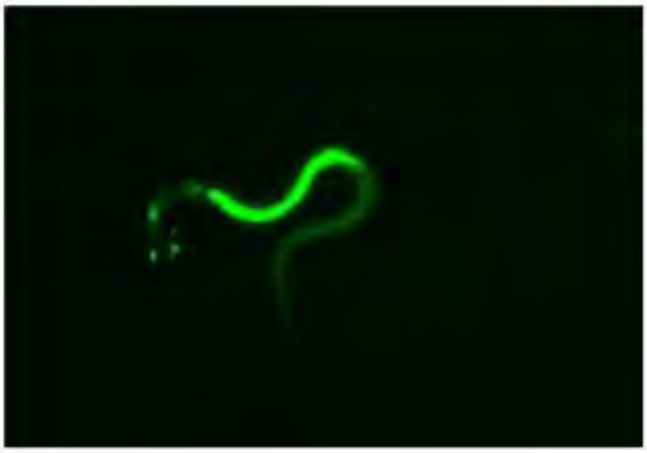


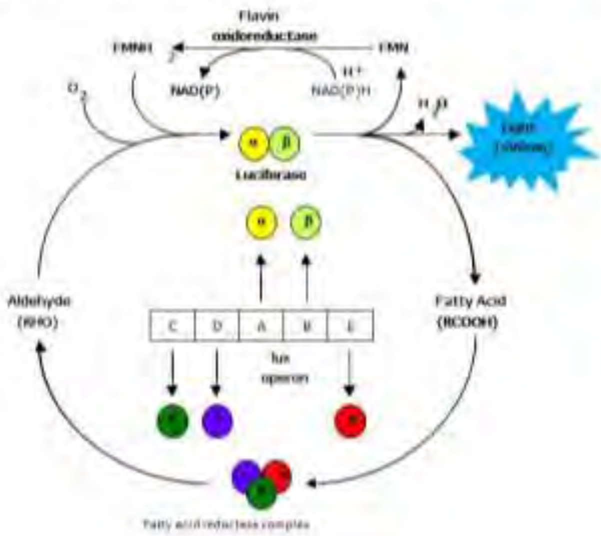
Image credit:

@SiouxsieW

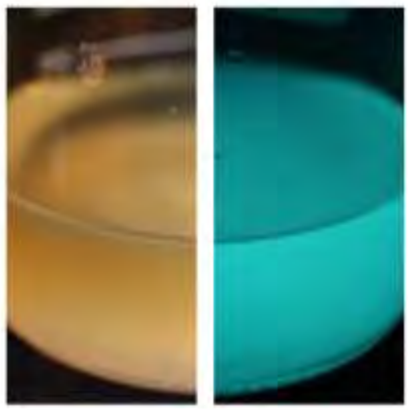
Part III

Bioluminescence & the 3Rs...

Bioluminescence:
a simple chemical reaction

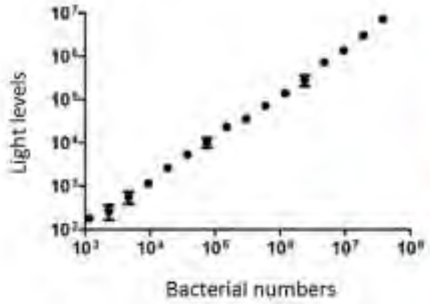


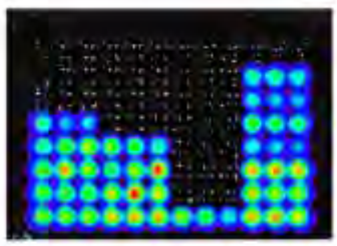
@SiouxsieW



@SiouxsieW

Counting live bacteria with light

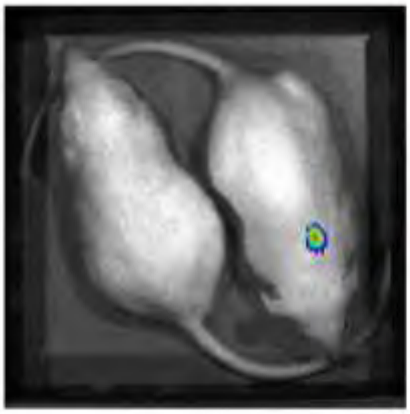




Dead or alive?

Answer in seconds/minutes rather than days/weeks/months!

@SiouxsieW



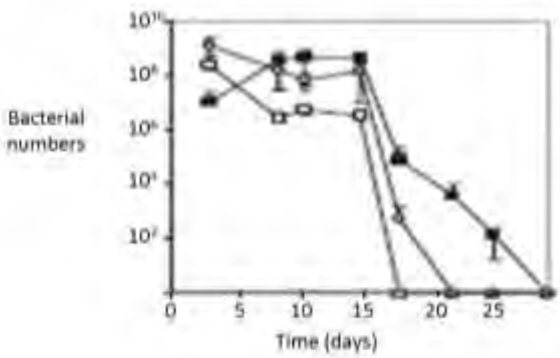
Giving mice food poisoning....

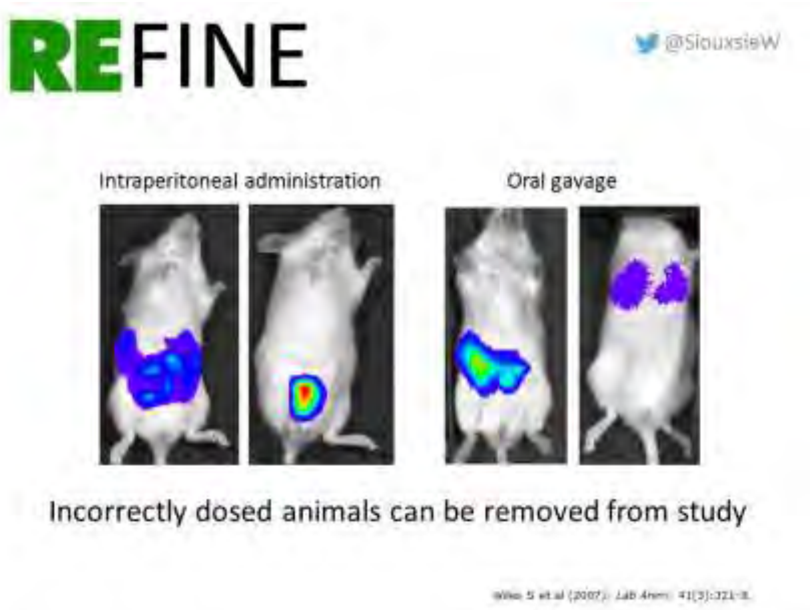
wellcome trust

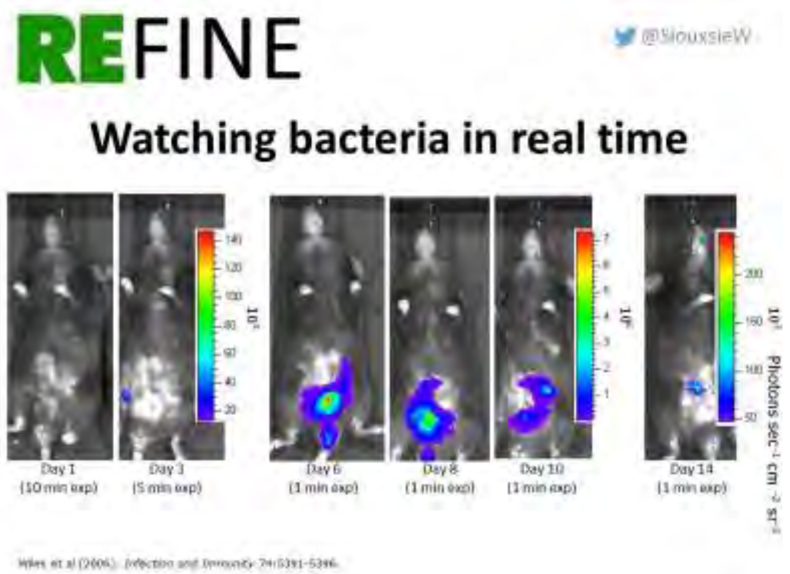
Image credit:
Bertola et al (2013) Nature Protocols 8: 627–637.
doi:10.1038/nprot.2013.032

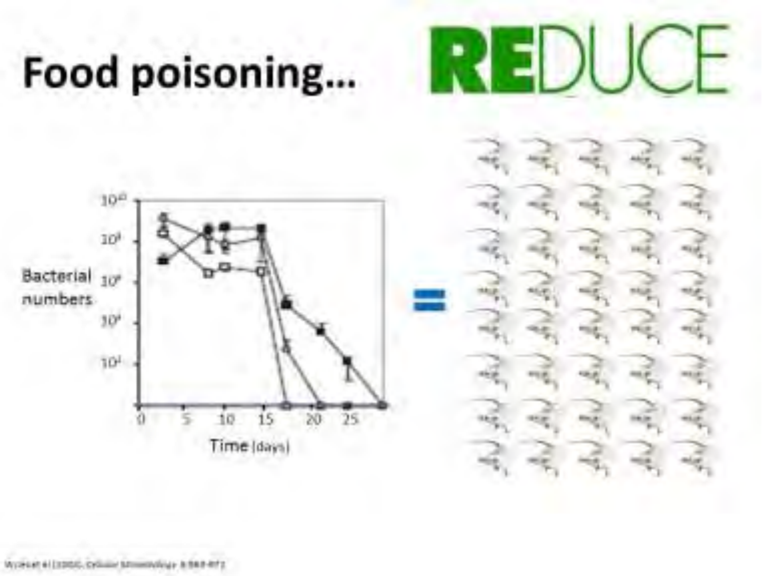
@SiouxsieW

Food poisoning in mice...



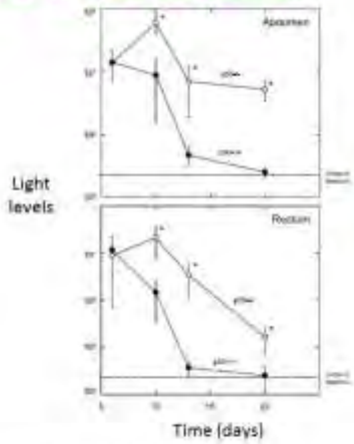

REFINE
@SiouxsieW
Intraperitoneal administration
Oral gavage
Incorrectly dosed animals can be removed from study
Wiles S et al (2007). Lab Anim. 41(3):321-8.


REFINE
@SiouxsieW
Watching bacteria in real time
Day 1 (10 min exp)
Day 3 (5 min exp)
Day 6 (1 min exp)
Day 8 (1 min exp)
Day 10 (1 min exp)
Day 14 (1 min exp)
Photons sec⁻¹ cm⁻² sr⁻¹
Wiles et al (2006). Infection and Immunity 74:5391-5396.


Food poisoning...
REDUCE
Bacterial numbers
Time (days)
0
5
10
15
20
25

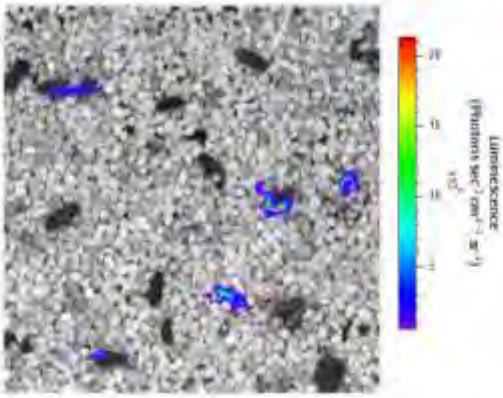
REDUCE

@SiouxsieW



Dennis et al (2008). Infection and Immunity, 76:4978-4988

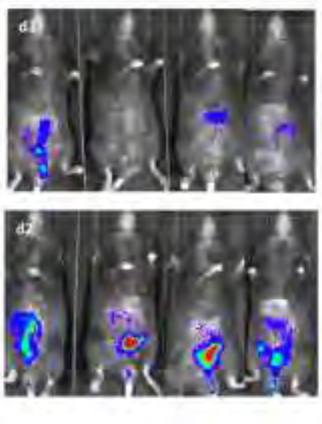
In one end… & out the other!



~100 million bacteria per mouse per day

REFINE

@SiouxsieW



NC3Rs

National Centre for the Replacement, Refinement and Reduction of Animals in Research

Wiles et al (2005). *Cellular Microbiology* 7:1163-1172
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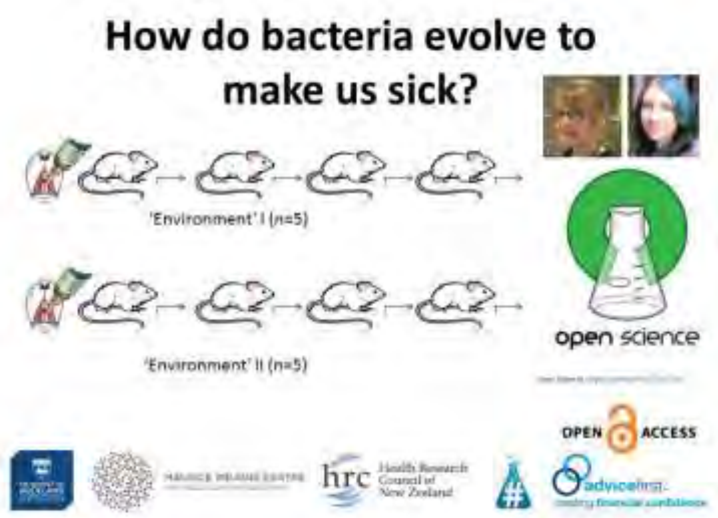
How do bacteria evolve to make us sick?
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hrc Health Research Council of New Zealand
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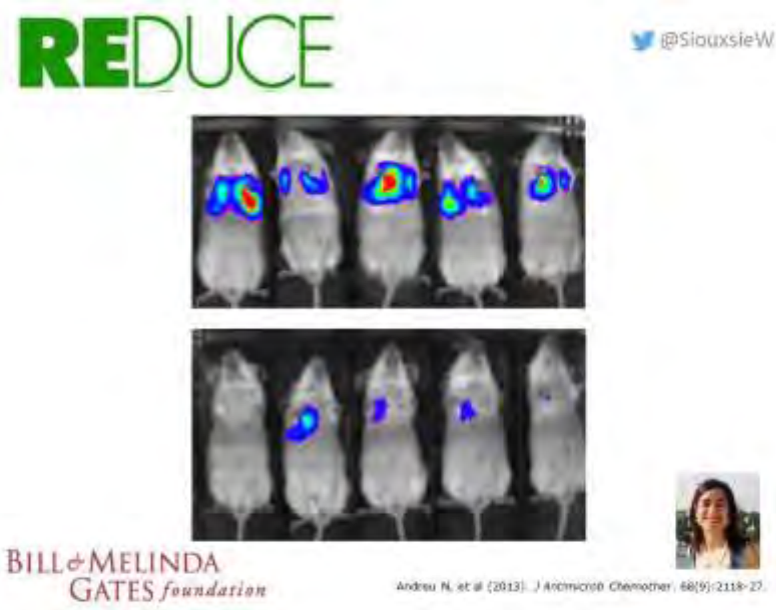
The "captain of death"...


REDUCE
@SiouxsieW
BILL & MELINDA GATES foundation
Andreu N, et al (2013). J Antimicrob Chemother. 68(9):2118-27.

Mr Simon Young

Orthopaedic Surgeon

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Infection of implants
96h after surgery

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Part IV

Replacement...

REPLACE

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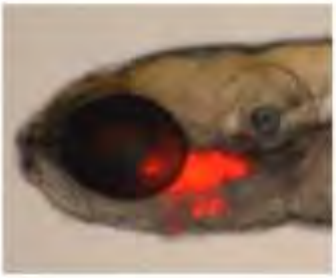

MAURICE WILKINS CENTRE


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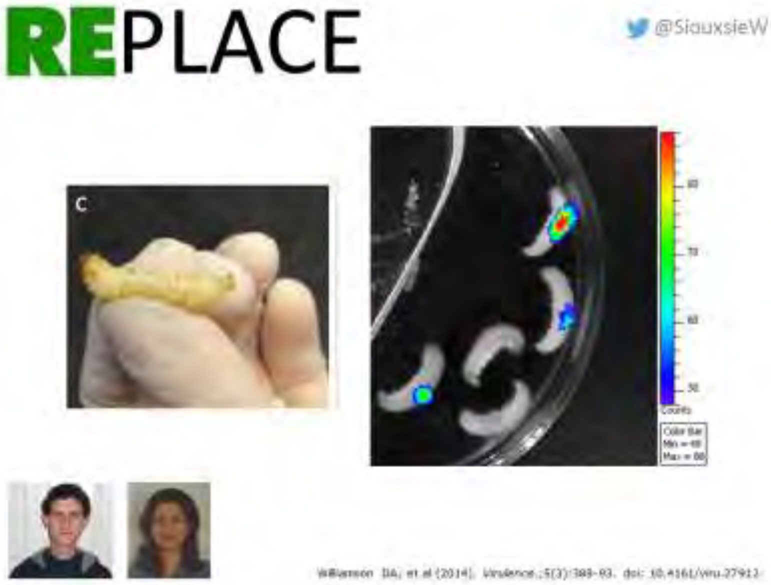
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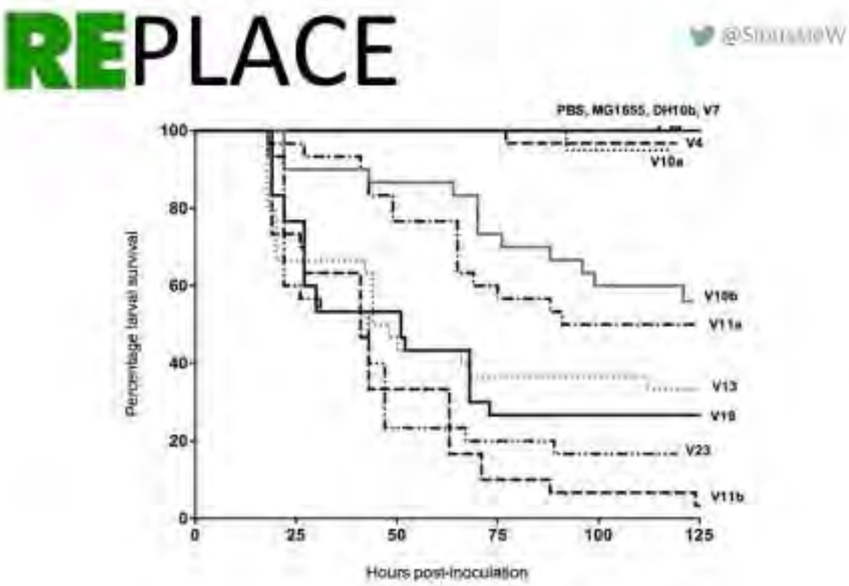
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PBS, MG1655, DH10b, V7
V4
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V23
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Percentage larval survival
Hours post-inoculation
0
20
40
60
80
100
0
25
50
75
100
125

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Dissecting distress: what is a humane death and how can we assess the humaneness of death in the context of Controlled Atmosphere Stunning?

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Welfare is a state within the animal itself and is often characterised as the outcome of the various mental experiences the animal has at a point in time, i.e. how it experiences what is happening to it. A key feature of this characterisation is that animals must be conscious to have mental experiences, meaning that their welfare can only be impacted upon when they are conscious (Mellor & Beausoleil 2015).

In order to safeguard the welfare of animals under our care, all aspects of their lives should be considered, including the potential impacts (humaneness) of the chosen killing method. The humaneness of death depends on three general features: the duration for which animals may have conscious experiences; the quality/type of negative experiences occurring during that time; and the intensity/severity of those experiences.

In the past, evaluations of animal welfare have often been centred on the absence of 'pain and distress' or 'pain and suffering'. Such composite terms are ubiquitous, appearing in scientific articles, guidelines and codes of practice, policy documents, legislation and the common vernacular. However, terms such as 'distress' and 'suffering' are rarely defined and are difficult to apply in a practical sense to evaluate welfare (Brown *et al*. 2006). In the context of laboratory animal use, distress has been defined as 'One or more negative psychological states indicative of poor wellbeing and/or that decrease animal's wellbeing and quality of life" (Brown *et al.* 2006). Similarly, suffering has been noted to include a wide range of unpleasant emotional experiences, the greater the duration and/or intensity of which, the greater the likelihood of suffering (Dawkins 1980). Thus, it is likely that the use of generic terms such as 'distress' and 'suffering' is aimed at covering all negative experiential bases and indicating the severe and/or prolonged nature of some or all of the various unpleasant experiences they encapsulate (Weary 2014).

However, the use of generic phrases such as 'pain and distress/suffering' can limit the accuracy of scientific welfare evaluations and lead to the 'no pain, no welfare problem' fallacy. For example, their usage can lead to under-emphasis of the importance of other unpleasant experiences that are qualitatively dissimilar from pain but which can be equally or more detrimental to welfare (e.g. air hunger), as well as to the failure to systematically look for, or recognise, indicators of such experiences. The 'no pain, no problem' paradigm is aptly illustrated by the general acceptance of gradual fill carbon dioxide (CO_2) as a humane alternative to rapid immersion in high CO_2 concentrations for stunning/killing laboratory animals. Mammals, including rodents, show aversion behaviours such as withdrawal and learned avoidance to CO_2 concentrations commonly used in gradual fill methods and which are much lower than those required to cause pain (e.g. Niel & Weary 2006, 2007); the observed aversion must thus reflect other experiences, such as air hunger or anxiety, which are qualitatively different to pain but which are unpleasant and impact on welfare nonetheless. Additional problems are that the use of 'distress' or 'suffering' does not facilitate understanding of what causes the aversion expressed by animals, nor how to specifically avoid or mitigate those experiences.

When evaluating the humaneness of killing methods, the kinds of information that can be cautiously used to systematically explore the types/qualities of negative experiences that may occur before loss of consciousness include: an understanding of the physiological/neurophysiological mechanisms of different unpleasant experiences and the effects of strategies known to circumvent or mitigate those specific experiences (e.g. analgesics for pain); observation of specific protective behavioural and physiological responses; and human reports of experiences during similar situations. The use of specific terminology and studies designed to investigate the occurrence of specific unpleasant experiences before loss of consciousness are needed to better understand the relative humaneness of various methods of stunning/killing animals.

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Ngaio Beausoleil is Canadian born but has spent more than half her life in New Zealand. She completed her PhD in animal behaviour, physiology and welfare at Massey University in 2006 and is currently senior lecturer and Deputy Director of Massey's Animal Welfare Science and Bioethics Centre. Ngaio's research focuses on scientific assessment of animal welfare and employs behavioural and physiological methods to investigate various aspects of welfare in farm, companion and wild animal species. Major research themes include:

- *Systematic scientific evaluation of animal welfare*
- *Extending our understanding of the range of negative experiences affecting animals' welfare, with particular interest in breathlessness*
- *Humane methods of 'euthanasia' particularly gaseous methods*
- *Welfare impacts associated with wildlife conservation activities including pest control*

Ngaio Beausoleil is currently the animal welfare science expert member of New Zealand Veterinary Journal Editorial Board and the Wellington Zoo Trust Animal Welfare Committee. She is also an independent scientific member of the New Zealand Animal Behaviour and Welfare Consultative Committee and the Massey University liaison for the Universities Federation for Animal Welfare. She teaches animal physiology to science and veterinary science undergraduates and supervises postgraduate research students.

ANIMAL WELFARE AOTEAROA

Dissecting Distress

What is a humane death and how can we assess humaneness of death?

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Animal Welfare Science and Bioethics Centre
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New Zealand

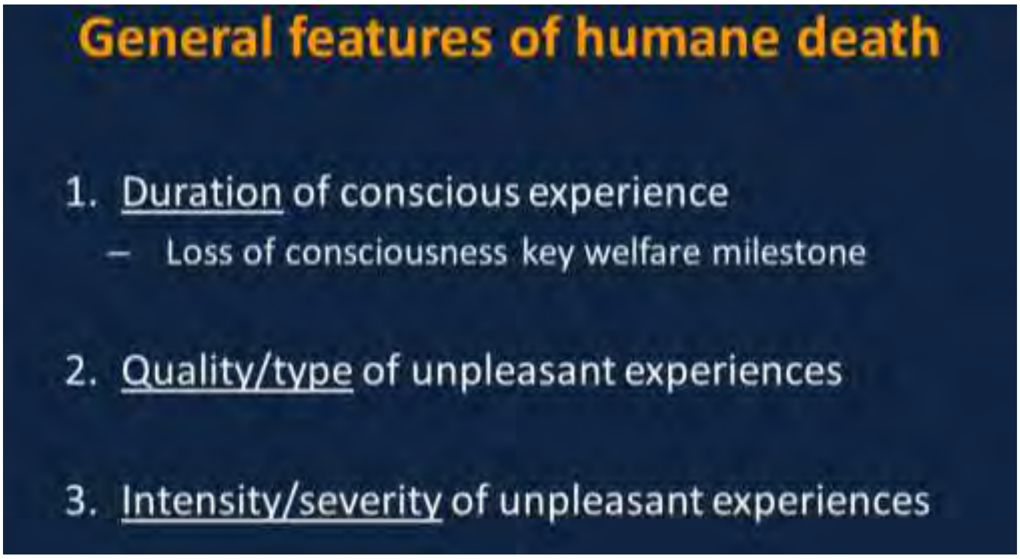
To be covered

1. What is animal welfare?
2. What is a humane death?
3. How can we assess humaneness of death?
   A. Specific descriptions of negative experiences before loss of consciousness
   B. Four categories of info for evaluating QUALITIES/TYPES of unpleasant experiences
4. Conclusions

1. Animal welfare characterized as....

- State within animal
- Integration of **mental experiences/affective states**
  - *Negative emotions ↓ welfare*
  - *Positive emotions ↑ welfare*
- Have to be **conscious** to have any experiences


2. What is a humane death?
Euthanasia = 'good death'
Two definitions in common use:
1. Technical approach and welfare implications
2. Above + Reason for killing (animal's best interest)
RTT context – #2 rarely applicable


General features of humane death
1. Duration of conscious experience
– Loss of consciousness key welfare milestone
2. Quality/type of unpleasant experiences
3. Intensity/severity of unpleasant experiences


3. How can we assess humaneness of death?
A. Dissecting distress (terminology)
• AWS traditional focus on negative experiences
• "Pain & distress" or "Pain & suffering"
• Aim: Cover all negative bases
• Reality: No pain = no welfare problem (fallacy)

Problems with generic terms

1. **Don't facilitate understanding of cause**

Distress: *"One or more negative psychological states indicative of poor wellbeing or that decrease wellbeing"* (Brown et al. 2006)

Suffering: *"Wide range of unpleasant emotional experiences"*
Greater duration/intensity increases likelihood of suffering (Dawkins, 1980)

Conclude:

- Both used to indicate BADNESS of various 1° unpleasant experiences
- But not what caused badness
- More useful to specify TYPE, DURATION & INTENSITY of 1° experience

Problems with generic terms

1. Don't facilitate understanding of cause
2. Don't facilitate targeted solutions

Problems with generic terms

1. Don't facilitate understanding of cause
2. Don't facilitate targeted solutions
3. Under-emphasize importance of other negative experiences *e.g. breathlessness*

Problems with generic terms

1. Don't facilitate understanding of cause
2. Don't facilitate targeted solutions
3. Under-emphasize importance of other negative experiences *e.g. breathlessness*
4. Fail to look for/recognize evidence of other negatives

"Pain & distress" or "Pain & suffering" → "Pain et al."

3. How can we assess humaneness of death?

B. Systematic evaluation of evidence

Do animals show aversion to method?

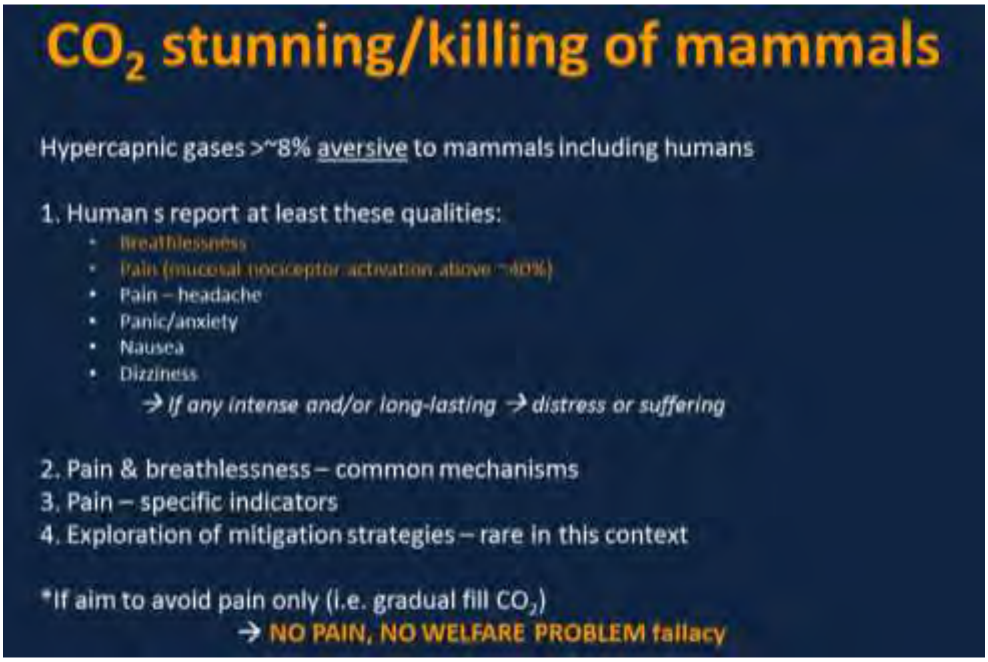
If yes: WHY?

1. Quality/type of unpleasant experiences
2. Intensity/severity of unpleasant experiences
3. Duration of conscious experience

Four categories of info for evaluating QUALITY/TYPE of negative experiences

1. Human report in similar situations
2. Understanding physiological/neurophysiological mechanisms
3. Observation of specific protective responses
4. Effects of strategies to circumvent/mitigate specific experiences

e.g. analgesics


CO_2 stunning/killing of mammals
Hypercapnic gases >~8% aversive to mammals including humans
1. Human s report at least these qualities:
• Breathlessness
• Pain (mucosal nociceptor activation above ~40%)
• Pain – headache
• Panic/anxiety
• Nausea
• Dizziness
→ If any intense and/or long-lasting → distress or suffering
2. Pain & breathlessness – common mechanisms
3. Pain – specific indicators
4. Exploration of mitigation strategies – rare in this context
*If aim to avoid pain only (i.e. gradual fill CO_2)
→ NO PAIN, NO WELFARE PROBLEM fallacy


4. Conclusions
1. Humane death/euthanasia - technical approach & welfare implications
2. Three general features for determining humaneness
3. Scientific assessment of humaneness of killing methods
– Specific terminology to discuss and study welfare impacts of killing
– 4 categories of evidence evaluate different QUALITIES of unpleasant experiences
4. Targeted strategies to reduce welfare impacts/improve humaneness


ANIMAL WELFARE AOTEAROA
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• ANZCCART for invitation to speak and ANZCCART-NZ for supporting 'Welfare impacts of CAS' 2017 international conference
Find us on @AnimalWelfareAotearoa

Compassion fatigue - the cost of killing

Arnja Dale, Jasmine Sawyers, Dr Sarah Zito
Animal Welfare Science & Education Department, RNZSPCA

Animal care workers such as veterinarians, vet nurses, laboratory animal workers and animal shelter workers are at an increased risk of developing compassion fatigue. Compassion fatigue is the emotional and physical exhaustion triggered by traumatic events, such as cruelty cases, major trauma events, or constant exposure to euthanasia, and is often referred to as 'the cost of caring' or the 'caring-killing paradox'. Compassion fatigue produces lower levels of job satisfaction, high employee turnover and generates a variety of physical and psychological symptoms ranging from mild to severe. Understanding of the risk factors, symptoms and methods to prevent compassion fatigue and assist people suffering from compassion fatigue are vital components of ensuring that animal care workers can continue to do their important work. Employers of animal care workers need to be aware of the risk factors for compassion fatigue in their staff and should ideally implement proactive strategies to help prevent compassion fatigue and assist those staff suffering from compassion fatigue.

Introduction

Compassion fatigue (CF) has been defined as the cost of caring (Figley 2002), or more specifically, the depletion of emotional resources from empathetically engaging with others who are experiencing emotional turmoil or pain (Holocombe *et al.* 2002). In terms of health professionals, Schwam (1998) defined it as "the emotional burden that health care providers may experience as a result of overexposure to traumatic events that patients are experiencing".

CF is considered a form of Post Traumatic Stress Disorder (PTSD), a condition that includes reliving a traumatic situation, avoiding situations that trigger related memories and experiencing physical distress when remembering the event (Figley & Roop 2006; Tiplady & Walsh 2013). However, in contrast to PTSD, CF is often difficult for the sufferer to identify because exposure to trauma is generally prolonged and cumulative, whereas PTSD is produced by specific events that can be easily associated with the development of the condition (Cohen 2007). CF is considered a type of PTSD caused by indirect exposure to trauma, so it is also referred to as secondary PTSD, Secondary Traumatic Stress (STS) and vicarious trauma (Cohen 2007; Huggard & Huggard 2008).

CF is also associated with two other health conditions: burnout and perpetration-induced traumatic stress (PITS) (Tiplady & Walsh 2013; Roberts 2015). Burnout is defined as the emotional and physical exhaustion generated by excessive pressure and decreased satisfaction (Figley & Roop 2006). Burnout results in similar physical effects to CF, such as headaches, sleep disorders and drug abuse (Tiplady & Walsh 2013). However, burnout is related to work stress, high cortisol levels and long working hours, whereas CF relates to low cortisol and a small hippocampus (the brain area that deals with memories and stress) (Cohen 2007).

PITS, in contrast to CF, is produced by actively participating in the completion of traumatic events (such as euthanising animals), and it is also considered a form of PTSD (Rohlf & Bennett 2005). Although PITS and CF present with similar symptoms, the appearance of CF does not require active participation in traumatic situations, whereas PITS does (Roberts 2015). Nonetheless, both conditions can occur simultaneously and interact to exacerbate distress in health care professionals.

Symptoms and prevalence

CF produces lower levels of job satisfaction and high employee turnover (Rogelberg *et al.* 2007) and also generates a variety of psychological and physical problems. However, since CF sufferers often perceive the associated mental and physical exhaustion as a measure of dedication and caring, affected people usually do not seek help until the symptoms have become extreme (Cohen 2007).

CF is a source of physiological long-term stress that triggers the “flight or fight” response that is the human body's primitive and automatic response which prepares the body to "fight" or "flee" from perceived attack, harm or threat to its survival. When the “flight or fight” response is triggered, a cascade of neurohormonal events occurs leading to physical and behavioural changes. As a consequence people suffering from CF may show contrasting behavioural coping strategies, such as dissociation and numbness to conserve energy or hypervigilance in preparation for “flight or fight”, as well as avoidance of duties, isolation or constant obsession with the traumatic event (Cohen 2007).

Mild psychological symptoms of CF include: loss of interest in work; frustration; lack of tolerance or confidence; and withdrawing from joyful activities and relationships. If unaddressed these mild symptoms can progress to more serious problems such as mood swings, conflict with friends and family, sleeping and eating difficulties, acute emotional pain, anxiety attacks, substance abuse, and even suicide (Mitchener 2002; Reeve *et al.* 2005, Durrance 2007).

Of those professionals at risk of developing CF, veterinarians are twice as likely to commit suicide than other healthcare professionals and four times more likely than a member of the general public (Bartram & Baldwin 2010). In New Zealand, a 2006 study identified that 15% of veterinary professionals had had serious thoughts about suicide, and 2% had already attempted suicide (Gardner & Hini 2006). A similar study based in Alabama found that 24% of respondents had considered suicide since they began veterinary training (Skipper & Williams 2012).

In addition to the aforementioned psychological issues, CF can produce a variety of physical problems such as high blood pressure, ulcers, and sleep disorders (Anderson *et al.* 2013). These health issues are related to a phenomenon known as Allostatic Load (AL), defined as the cumulative physiological effects of the body’s efforts to adapt to chronic stress (Glover et al 2006). Chronic stress in relation to work exhaustion has been proven to initiate genetic processes, such as the decrease of telomere length (Ahola *et al.* 2012). Telomeres are protective nucleotide sequences at the end of chromosomes that protect against chromosomal damage. Telomere shortening has been associated with ageing, cancer, diabetes and poor clinical outcomes from disease (Ornish *et al.* 2008; Ahola *et al.* 2012). Care-giving professionals such as nurses have been highlighted as high-risk populations for AL development due to CF, making them more vulnerable to the physiological and genetic damage of chronic stress (Clark 2014).

Compassion fatigue and animal care professionals

While compassion and empathy are great assets for care-giving professionals working with animals, the constant necessity to alleviate distress in animals and other people increases the risk of developing CF (Tiplady & Walsh 2013). Animal care professionals must cope with occupational situations such as non-compliant clients, time demands, high number of work hours and professional liability as well as other factors that contribute to increased stress levels (Figley & Roop 2006; Bartram *et al.* 2009). Furthermore, personal concerns about insufficient training and skills, high professional standards and feelings of underachievement are common stress related factors in these occupations that contribute to CF (Figley and Roop 2006, Mitchener 2002). In New Zealand, the greatest sources of work-related stress for veterinary staff have been identified as client expectations, long work hours, and professional development (Gardner & Hini 2006). In addition, animal care work is generally undervalued by society and is also generally poorly paid (Hammid 2005). This may contribute to strain by diminishing a positive sense of self and social validation (Reeve *et al.* 2005).

In addition to occupational work-stress, most animal care professionals must cope with the so called "caring-killing paradox", which requires people that deeply care about animals to kill animals on a regular basis (Arluke 1994). In fact, animal care professionals perceive euthanising animals as one of the main causes of occupational stress (Rohlf & Bennett 2005). The need to participate in euthanasia and other traumatic events generates the conditions to develop PITS and enhance the effects of CF, although CF doesn't require participation on animals' euthanasia to appear (Roberts 2015).

Veterinary Staff

Veterinary staff are under a great deal of pressure as they must meet the medical needs of their animal patients but must also support their clients emotionally. With the advancement of technology and skills, veterinarians are able to comply with owners' requests to go to greater lengths to treat or prolong the lives of animals, whereas in the past similar circumstances may have simply necessitated euthanasia (Cohen 2007). This greater investment in the owner and animal presents a more complex emotional attachment and contributes to the development of CF after euthanasia for vet staff. Furthermore, the juxtaposition of clients who want to prolong their pets' life or are mourning an animal and requiring emotional support and, in contrast, the clients who want to euthanise a healthy pet for convenience is a source of ethical stress for veterinary staff (Black *et al.* 2011). In addition, the continuous exposure of veterinarians to death and euthanasia of animals generates continuous feelings of grief; these may have varying duration and effects depending on the individual (Tiplady & Walsh 2013).

Nonetheless, it has been found that stress, burnout, and job dissatisfaction decreases with the time from graduation (Fritschi *et al.* 2009; Hatch *et al.* 2011; Ballantyne 2015). This may be a contributing factor in dissatisfaction with careers and veterinary staff eventually leaving the profession (Reijula *et al.* 2003). Job dissatisfaction and burnout are mostly reported in the first five years after graduation (Hatch *et al.* 2011) making this period critical for the development of coping strategies. However, more research is needed to understand the kind of coping strategies veterinary staff develop on their own and the type of personality traits that make people more likely to remain in the profession, regardless of the risk to develop CF.

Shelter Staff

Shelter staff experience great guilt in euthanasing healthy animals (Arluke 1994) as well as anger at society for relinquishing and not wanting their animals (Rollin 2011). Shelter management has reported anger in approximately two out of every three staff members, as well as sadness (83%), crying (68%), depression, irritability, and grief (52-57%) when euthanasing animals (Anderson *et al.* 2013). In one study that asked shelter staff whether euthanasia contributed to their burnout, 74% agreed or strongly agreed (Reeve *et al.* 2005). The same study found that shelter staff directly involved in euthanasia reported higher levels of work stress, stress-related physical symptoms, work-family conflict, and reduced job satisfaction compared to those who were not directly involved. Hence, shelter personnel practising euthanasia are more likely to have a combination of PITS and CF.

Shelter staff can cope with CF and PITS by adopting attitudes that rationalise the event in a positive light. Studies have reported that shelter staff understand the need to perform euthanasia, with half of the respondents in one study feeling like they were performing a beneficial act (Anderson *et al.*

2013), and knowing that it was the best option for the animal (Baran *et al.* 2009). These attitudes are associated with lower levels of job dissatisfaction (Reeves *et al.* 2005). Likewise, improved education and awareness of the positive impacts animal care workers are having (both within organisations and publicly) could help to mitigate negative perceptions about their job (Scotney *et al.* 2015).

Laboratory technician and scientists
Scientists and animal technicians involved in studies that require animal use and euthanasia also report symptoms of CF, such as depression, anxiety, sleep loss and increased alcohol consumption, with underlying themes of discomfort, uneasiness and guilt (Davies & Lewis 2010). Nonetheless, talking about these feelings is frowned upon in the scientific profession and generally little or no institutional support is given (Arluke 1992, 1996). Bioterium (animal facility) technicians and scientists can develop deep relations with the animals at their care. Nonetheless, they are encouraged to see the animals as objects and sometimes, reprimanded when providing higher levels of care, such as enrichment and special food items (Arluke 1992). Likewise, showing emotions or unwillingness to perform euthanasia are negatively perceived by peers, which contributes to high levels of emotional dissonance (Davies & Lewis 2010). Studies have shown that support from peers is crucial in coping with euthanasia of experimental animals. For scientists and animal technicians, an important coping mechanism is being able to rationalise the purpose of their occupation (such as believing that their duty has a greater social value or that euthanasing animals is not dissimilar to the use of animals in other contexts) (Arluke 1992; Davies & Lewis 2010).

Farmers
Farmers can also experience CF, as they also develop strong relationships with the animals under their care. Chur-Hansen (2010) highlighted the grief that farmers and their families can experience when they lose livestock animals. This can result in feelings of guilt, shame, grief, and failure, and can be particularly devastating when the animals are healthy but must be destroyed due to a lack of feed or water. Culling of livestock has also been associated with PTSD (Olff *et al.* 2005), and suicidal thoughts and acts (Peck 2005); this can put farmers at high risk of developing PITS, CF or both.

Slaughterhouse workers
Slaughterhouse workers have significantly higher rates of physical and psychological disturbance compared to a comparable group of office workers and meat packers. These problems include phobic anxiety, anger, hostility and psychosis (Emhan *et al.* 2011). Absence from work has been reported as a coping strategy used by slaughterhouse workers and is more common in workers with higher job strain (Kristensen *et al.* 1991). Due to the nature of the work, it has been suggested that it is difficult to know whether these effects are a result of the work or were antecedent, as some employees have reported that they came to enjoy the killing over time (Dillard 2007). Emhan et al. (2011) observed that those slaughterhouse workers who suffered depression and anxiety were more likely to have feelings of remorse, whereas brutal behaviours were associated with anger and hostility, implying that although some slaughterhouse workers may have previous tendencies towards violence and lack of compassion, others develop CF-related problems through their job and these need to be addressed.

Prevention and treatment

Risk factors
Regardless of the area of animal care that a person is involved in, from the veterinary profession to laboratory work, there is little difference in the types of symptoms experienced among the occupational sub-sets (Scotney *et al*. 2015). However, not all individuals in those situations will experience CF and symptoms vary between individuals and the effectiveness of different treatments is also likely to vary between individuals.

The most important risk factors identified as associated with the development of CF are:

- The duration and number of traumatic events that the person is exposed to/involved with;
- The context and individual-related factors such as attitude and available support systems (Rohlf & Bennett 2005);
- Personal or family histories of psychological illness, abuse or trauma (Breslau 2001).

Tools for reducing compassion fatigue and perpetration induced traumatic stress

There are three kinds of tools that can be implemented to reduce CF and PITS in animal care workers:

Environmental support strategies

Modifying the work environment to reduce sources of stress has been proven effective for nurses working in acute care nursing settings (Mimura & Griffiths 2003). For animal care professionals, staff rotation, breaks following euthanasia tasks and comfortable and private rooms to perform euthanasia were amongst the strategies that shelters have used to try and reduce stress. Other strategies such as education and counselling were seen as too financially demanding (Anderson *et al.* 2003).

Shorter and more frequent sessions of euthanasia were recognised as more emotionally taxing than longer but less frequent sessions (Reeves *et al.* 2005). Therefore, reducing the frequency of euthanasia participation (even if each session was longer) could be another an environmental management tool that could be applied to manage euthanasia-related stress.

Education and information

In a study evaluating support systems in shelters, stress and coping seminars were ranked as the number one support system desired by shelter staff. Nonetheless, such sessions were only provided in 11% of the facilities surveyed (Anderson *et al.* 2013). Similarly, Rohlf & Bennett (2005) reported that, in a sample including veterinarians, veterinary nurses, and research and animal shelter staff, only one quarter of the participants had received specific training in grief counselling or stress management. They concluded that good husbandry and management skills are not enough to equip people with appropriate coping skills.

It has been demonstrated that the ability of veterinary staff to establish a rapport with their clients allows the discussion of difficult subjects, and this helps to improve client compliance and reduce negative aspects of the role (Ballantyne *et al.* 2015). Despite the importance of this skill, in this study less than 50% of veterinary staff had any formal training in client communication and nearly every respondent had difficulty in this area. Therefore, this may be another area where education would benefit both veterinarians and veterinary clients (Ballantyne *et al.* 2015).

Formal and informal support sources

Although shelter staff have identified counselling and support groups as valuable to cope with stress, they were only offered in 3.7% of the facilities surveyed in a study performed in the USA (Anderson *et al.* 2013). Perhaps because of this lack of institutional support, it has been reported that shelter personnel generally rely on their own coping skills and informal support from family and friends (Baran *et al.* 2009).

Informal counselling has also been found beneficial in helping to manage stress in animal-care professionals. For example, in one study, self-help groups in which mutual support and encouragement were offered, were mentioned as the most important source of help for euthanasia-related stress by animal-care professionals (Rogelberg *et al.* 2007). Another alternative tool that has been proven effective is journaling, as creative writing can help people to express and make sense of their feelings (Pennebaker & Seagal 1999; Unsworth *et al.* 2010). Finally, online support through Facebook has also been found to be a support group tool to handle stress (Anderson *et al*. 2003) and research on the benefits of this kind of support has shown that it can offer empowerment, disinhibition to share sensitive experiences and feelings, and can help to connect people in need (Barak *et al.* 2008, Rains & Young 2009).

In terms of formal counselling, the introduction of Balint groups has been shown to be successful in treating and preventing CF and burnout (Benson 2005). A Balint group is professional counselling led by a psychiatrist, where case studies of situations that invoke a distressing response in its members are analysed. The aim is for members to recognise that they are not alone and to increase their capacity to deal with difficult situations. Traditionally used by health-care professionals, Balint groups could be used to help animal-care workers either within their organisations or outside of the organisation through the Balint Society of New Zealand and Australia (Huggard 2008).

Prevention and management of compassion fatigue

Appropriate environment, education and support to prevent and treat CF require implementation at three levels (Huggard 2008):

Organisational level
Organisation size has been related to reduced stress-related factors and increased job satisfaction indicating that larger or private facilities might have more resources to support their staff compared to government-owned facilities (Reeves *et al.* 2005). In addition, staff perception that their organisation helps to prevent animal welfare issues by participating in community outreach programmes or education for responsible pet ownership has also been seen as a good tool to combat compassion fatigue in staff (Baran *et al.* 2009).

Organisations that implement environmental management, such as additional staffing, job rotation, training in coping skills and euthanasia, and support from colleagues and professionals greatly improve the working conditions of their staff (Rogelberg *et al.* 2007). Nonetheless, the aforementioned lack of counselling and support groups is a concerning factor that should be addressed at organisational level with little financial investment (Anderson *et al.* 2003).

Peers and colleagues
Creating or participating in a supportive peer group has also been shown to be effective in treating CF, whether it is social outings, organising staff meetings to discuss concerns or feelings or presenting complex and difficult cases (Huggard 2008).

One study found that employees who felt their contributions and wellbeing were valued by their co-workers experienced health benefits, more job satisfaction, and were less likely to feel depressed (Bradley *et al.* 2002; Byrne *et al.* 2005). Acknowledgement of the positive contributions of workers' roles and support from peers have been found to help prevent or reduce CF in animal-care workers consistently across several studies (Reeves *et al.* 2005; Baran *et al.* 2009; Anderson *et al.* 2013).

Personal care
Methods suggested to help reduce compassion fatigue include taking care of oneself, having fun on a regular basis, spending time in nature, finding a relaxation technique, changing one's attitude towards the stressors, and asking for help (AVMA 2004). Likewise, proactive behaviours such as exercise, good nutrition, hobbies, taking part in activities in which one can excel, respecting one's

own limits, maintaining self-care and spirituality are regarded as good personal strategies to avoid CF and burnout (Benson 2005).

Self- management routines such as checking that tasks are finished, summarising the day before leaving, formally acknowledging the end of the workday, and not working at home are also methods that can help to reduce the stress of work. Separating personal life from work can help to make private experiences a source of positivity to support work rather than work negatively affecting home life (Baran *et al.* 2009). Other personal strategies that have been reported as successful by animal-care workers include talking to and comforting animals during care, focusing on the positive outcomes of their role, and maintaining a distant yet compassionate approach towards animals (Baran *et al.* 2009).

Conclusion

Compassion fatigue and the associated psychological and physical problems are a significant concern in animal care professions. An understanding of the risk factors, symptoms and methods to prevent CF and assist people suffering from CF are vital components of ensuring that animal care workers can continue to do their important work. Animal care organisations should be aware of the risk factors for CF in their staff and should implement proactive strategies to help prevent CF and assist those staff suffering from CF.

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