





Theme 3

Moral issues of animals, alternatives and public policy

Session 3.1

Influencing and making public policy

Funding for Research, Development, Validation and Acceptance of Alternatives Must Become Transparent

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Summary

Attempts to ascertain the amount of funding available worldwide for research, development, validation and, ultimately, acceptance of non-animal and other alternatives have been stunted by the lack of coordinated accounting and a centralised database. In order to prioritise replacement methods and also identify immediate needs in the field of alternatives, an electronic document or database must be collated on an annual basis to provide genuine transparency of federal and other funding. Federal regulatory and research agencies in the United States, European Union, Japan and other countries should agree to a pilot project. Additional funding data should be provided by the regulated industries, public and private scientific organisations and the animal advocacy community.

Keywords: funding, non-animal methods, alternative methods

Introduction

The purpose of this paper is to provide a window into the funding of research, development and validation of non-animal and other alternatives by some federal governments, the regulated industry, independent scientific institutions and the animal advocacy community. The relative paucity of information reveals the necessity for a coordinated, annual approach to collating and categorising accurate information. Accurate information regarding the amount of funding, the projects funded and their direct application to replacing, refining or reducing animals in regulatory toxicity testing is necessary to provide a mechanism for measuring commitment and success in this area.

Methods

The primary methods for obtaining information were websites and direct communications with federal regulators, members of industry and animal advocacy organisations. While industry, the

private and public science sector and animal advocacy organisations tend to track annual funding, it is difficult, if not currently impossible, to break out the spending by federal agencies in the United States. The European Union provides more specific information, but still does not readily itemise the particular projects. Contacts with Japan did not yield definitive results.

Results

The Federal Governments – Regulatory and Research Agencies: United States Environmental Protection Agency – The United States Environmental Protection Agency (EPA) serves as one case study in this area. After protracted negotiations with the animal advocacy community, led by the Doris Day Animal League and People for the Ethical Treatment of Animals, the EPA provided \$500,000 over a two-year period for research, development and validation of non-animal, alternative test methods. In addition, the National Institute of Environmental Health Sciences committed to \$4.5 million over the same fiscal years, 2000-2001.¹



Following this commitment, the Doris Day Animal League and other animal protection organisations lobbied the United States Congress to secure an appropriation of \$4 million in the EPA's Science and Technology Account under the Office of Research and Development for fiscal year 2003 for research, development and validation of non-animal, alternative test methods. This effort was led by Chairman James Walsh of the House Subcommittee on VA, HUD and Independent Agencies Appropriations and resulted in the first-ever congressional directive to the agency in this area.² It should be noted that between the fiscal years of 2003-2006, the EPA's Science and Technology Account has hovered between \$500-700 million. This is clearly noteworthy as the fiscal year commitment of \$4 million was less than one percent of the total research budget.

The EPA's Computational Toxicology Program received strong support from Congress through increased appropriations until fiscal year 2006. Certainly, it can be contended that a portion of this budget under the Office of Research and Development at the agency is directed at non-animal and other alternative test method development and potentially validation.³

Unfortunately, even after numerous attempts by animal protection organisations and letters from members of Congress requesting the EPA provide an accounting of how the various funds were expended, a satisfactory explanation has not been received. However, report language in the fiscal year 2006 EPA appropriations bill supported by the American Chemistry Council and the Doris Day Animal League specifically requires the agency to report back to Congress by early 2006 with an accounting of these expenditures.

United States National Institute of Environmental Health Sciences (NIEHS) – The entire fiscal year 2005 budget for NIEHS, including the National Toxicology Program (NTP), hovers at approximately \$650 million, which is a small portion of the overall EPA budget. In fact, it is merely equal to EPA's research budget.⁴ The significance of this disparity in funding is that the NTP is relied on by most United States federal regulatory and research agencies as the entity to characterise both acute and chronic exposures to chemicals, including a vast carcinogenicity database.

The NIEHS houses the National Interagency Center for Alternative Methods (NICEATM) for the Interagency Coordinating Center for the Validation of Alternative Methods (ICCVAM), which was permanently codified by Public Law No. 106-545.⁵ Essentially, the ICCVAM receives its funding from two sources: NIEHS provides approximately \$2.6 million per fiscal year; and federal agencies may contract for work through interagency agreements, much like EPA did with *in vitro* methods for its Endocrine Disruptor Screening Program. As the ICCVAM's function is not research and development, but evaluation of alternative and new or revised animal tests, its needs will arise with the number of methods in its pipeline.

European Union – The European Center for the Validation of Alternative Methods (ECVAM) has a broad mandate under existing law. It performs a centralised prioritisation, research, development, validation and recommendations regarding acceptance function. The 2003-2006 European Union Framework Programme 6 funds ECVAM at 35.2 million Euros for validation activities and 22.6 million Euros for methods development.⁶ ECVAM is responsible for cultivating and finalising alternative methods for a variety of legislative and regulatory mandates, including the cosmetics directive and the pending REACH programme.

It should be noted that the European Parliament in a November 2004 analysis of the 6th Framework Programme funding for the entity stated, "The political demand for alternative methods is high but must be underlined that ECVAM is only one link in the chain leading from the development of alternative methods to their regulatory acceptance."⁷

To that end, the European Union has a variety of national government centers that focus on alternatives. A few include the Centre for Documentation and Evaluation of Alternatives to Animal Experiments (ZEBET) under the German Bureau for Risk Assessment. ZEBET has expended a total of 5.5 million Euros for research in the alternatives area.⁸ Also of note is the United Kingdom's new National Centre for the Replacement, Refinement and Reduction of Animals in Research. It awarded 8 projects for approximately 1 million pounds in 2005.⁹

The regulated industry

Industry has long played a role in funding alternatives development and several of the accepted alternatives had their inception in industry-funded laboratories. A few companies specifically tout their long-term leadership in this area on their websites and in other communications, including The Procter & Gamble Company, Colgate-Palmolive and the United States trade association the Cosmetic, Toiletry and Fragrance Association (CTFA). The Procter & Gamble Company has invested approximately \$190 million and supported more than 50 proven methods, according to its website.¹⁰ In addition, it provided three grants at \$25,000 each in 2005 under a newly-focused program in this area. Colgate-Palmolive awarded grants in the range of \$10,000-40,000 in 2005 and consistently funds post-doctoral fellowships at \$33,500.¹¹ CTFA provided a three-year, \$1 million per year grant to The Johns Hopkins School of Public

¹ Wayland, Susan H., Deputy Assistant Administrator, Environmental Protection Agency letter to participants in United States High Production Volume Challenge Program, October 14, 1999.

² Report Language in House VA, HUD and Independent Agencies Appropriations Bill for fiscal year 2003, H.R. 2620.

³ Report Language in House VA, HUD and Independent Agencies Appropriations Bills for fiscal years 2004, 2005 and Report Language in House Interior Appropriations Bill for fiscal year 2006.

⁴ <http://thomas.loc.gov> and <http://niehs.nih.gov>

⁵ United States Public Law Number 106-545, <http://thomas.loc.gov>

⁶ European Commission Directorate General Joint Research Centre Communication, March 25, 2003, Hartung, Thomas, Head of Unit, ECVAM correspondence on August 9, 2005.

⁷ Hartung, Thomas, Head of Unit, ECVAM correspondence on August 9, 2005.

⁸ www.bfr.bund.de/cd/1591

⁹ www.nc3rs.org.uk/page.asp?id=30

¹⁰ www.pg.com/science/ria_approach.jhtml

¹¹ <http://altweb.jhsph.edu/databases/funding3.htm>



Health Center for Alternatives to Animal Testing in 1981-1983. It also provided a grant to the same entity in 1984 at \$700,000, with "continued funding in subsequent years."¹²

Private/public science Sector

Activity in this area in the science sector outside of the federal governments and industry has burgeoned worldwide in the past decades, including through the Institute for *InVitro* Sciences (IIVS), the Dr. Hadwen Trust for Humane Research, the Swedish Fund for Research Without Animal Experiments, the Fund for the Replacement of Animals in Medical Experiments (FRAME) and The Johns Hopkins School of Public Health Center for Alternatives to Animal Tests (CAAT). IIVS, which is based in the United States, has expended \$10.3 million between 1997 and 2005.¹³ This amount includes research and development and actually running methods to generate data to publish to boost the number of companies that use the methods. To date in 2005, the Dr. Hadwen Trust expended over 250,000 pounds.¹⁴ FRAME's 2003-2004 annual report states that it spent 361,363 pounds on research. The Swedish Fund for Research Without Animal Experiments, a private fund also funded by public donations, awards grants each year totally approximately 1-1.5 million Euros.¹⁵ Finally, in this brief analysis, the CAAT estimates it funded 300 grants between 1981-2005 for \$5.5 million.¹⁶

Animal advocacy foundations or organisations

Non-profit organisations have played a significant role in funding non-animal and other alternatives development over the years. Animal organisations, largely funded by individual donors and subject to the scrutiny of non-profit reporting, are often more transparent than other funding sources.

People for the Ethical Treatment of Animals is funding numerous projects between 1998-2007 for approximately \$590,000.¹⁷ The American Fund for Alternatives to Animal Research, founded by Dr. Ethel Thurston who is a true pioneer in this area, has channeled \$1 million into research and development since 1977.¹⁸ The Humane Society of the United States, with more than 9 million supporters and constituents, provides a stipend of \$5,000 every three years with its Russell

and Burch Award.¹⁹ The Alternatives Research Development Fund issues approximately \$150,000 each year.²⁰ And the Doris Day Animal League provides up to \$5,000 on an annual basis for special projects.

Discussion and conclusions

The lack of easily accessible and collated information from the various federal agencies or competent authorities hinders the overall ability to deliver a clear picture of the worldwide situation. In the United States alone, there are 15 federal regulatory and research agencies with a variety of individual programs that support both extramural and intramural research. While a few of the agencies have been influenced either internally or externally to set aside directed funding, it is imperative that an integrated, worldwide approach to prioritisation of endpoints, funding for research, development and validation of non-animal and other alternative test methods and a genuine push for their acceptance occur. It is vital to growing the science.

The private scientific sector is providing considerable funding for research and development of alternative methods, but due to their individual mandates and interests there is not a co-ordinated approach to focusing on specific endpoints or even areas of research. The same concern pertains to the animal protection organisations. While the organisations have a tendency for dialogue among themselves, often the projects to be funded are not the focus of discussion, rather the emerging science as a whole.

By the 6th World Congress on Alternatives and Animal Use in the Life Sciences, the various federal entities, industry, the private scientific sector and animal protection organisations should create a collective document clearly delineating the funding spent to research, develop, and validated non-animal and other alternative methods. There should be a direct attempt to track this funding from the point when a method demonstrates potential relevance to a specific endpoint, instead of lumping together all spending from very early stages of research.

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¹² www.ctfa.org/Content/NavigationMenu/About_CTFA/History/History_4.htm

¹³ Curren, Rodger, President of the Institute for InVitro Sciences correspondence on August 17, 2005.

¹⁴ Langley, Gill, Scientific Advisor for Dr. Hadwen Trust for Humane Research on July 25, 2005 and www.drhadwentrust.org.uk

¹⁵ www.stifud.se/print.php?filename=english/index.php

¹⁶ <http://altweb.jhsph.edu/databases/funding3.htm>

¹⁷ Seidle, Troy and Sweetland, Mary Beth, People for the Ethical Treatment of Animals correspondence on August 8, 2005.

¹⁸ <http://altweb.jhsph.edu/databases/funding3.htm>

¹⁹ www.hsus.org/ace/12630

²⁰ Leary, Sue, President of the Alternatives Research Development Fund in correspondence on August 8, 2005.



The OECD Health Effects Test Guidelines for REACH Need Updating

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Summary

Each OECD Health Effects Test Guideline has been analysed for suitability to be used in the REACH system for chemicals testing. Some TGs are unnecessary while others urgently require updating to include modern techniques for improving the scientific and animal welfare aspects of the procedures involved. The reasons why the TGs have become so outdated are discussed and recommendations are made for improving this unsatisfactory situation. It is recommended that the OECD and its international experts focus more on revising outdated, and deleting obsolete, TGs.

Keywords: OECD test guidelines, REACH, revision, deletion, three Rs

Introduction

Background to REACH

The European Commission (EC) issued a White Paper in 2001 entitled *Strategy for a Future Chemicals Policy*, aimed at ensuring greater protection of human health and the environment (Anon., 2001; Combes, 2004a; Warbrick and Evans, 2004) and to harmonise the way in which risk assessments are conducted for new and existing chemicals. This policy requires risk assessments to be undertaken for existing and new chemicals, prior to their regulation according to a new registration and evaluation scheme, REACH (Registration, Evaluation and Authorisation of Chemicals). The REACH legislation also shifts the burden of responsibility from regulatory bodies to industry to demonstrate the safety of chemicals. Industry will be required to submit detailed information on individual substances, including hazard property data, classification and labelling information, up to date safety sheets, and use and exposure information across the supply chain.

The European Commission issued its formal draft proposals for REACH which were adopted in October 2003, including the suggestion to create a new European Chemicals Agency to implement the REACH System in conjunction with the Competent Authorities (CAs) in Member States and the Commission Services (Dandrea and Combes, 2003). These proposals were issued in the form of an internet consultation and prompted many concerns on the part of industry and animal protection and welfare groups. They also contained a number of annexes, among which was one that included all the OECD Health Effects Test Guidelines, on the presumption that these would be required to be used for obtaining hazard information on chemicals under the REACH legislation.

The OECD Health Effects Test Guidelines

The OECD Test Guidelines (TGs), a collection of methods recommended to assess the hazards of chemicals, preparations and products, are intended to harmonise toxicity testing and to estab-

lish minimal standards. The OECD considers its TGs to be '*...the standard reference tool for chemical testing*' (preamble to TGs).

We have previously conducted a critical appraisal (Combes et al., 2004; Combes, 2004b) of the suitability of the TGs for REACH and found that several are in urgent need of revision with respect to techniques and replacement, reduction and refinement strategies (Balls et al., 1995). More information regarding these deficiencies and suggestions for improving the OECD TGs Programme are now presented.

Analysis of the OECD Health Effects TGs

Unnecessary TGs

Several TGs are not required for REACH (tab. 3 in Combes et al., 2004). Thus, TGs 401 and 406 (acute oral toxicity – LD₅₀ method and skin sensitization, respectively) have been superseded by improved *in vivo* protocols. TG 401 has been withdrawn by the OECD and replaced by 420, 423 and 425E. TGs 404, 405, and 427 (the corrosion part of acute dermal irritation and corrosion, acute dermal photoirritation, and dermal absorption, respectively) have been replaced by validated and endorsed *in vitro* methods. 415 and 476–485 (one generation reproduction study and various genotoxicity assays, respectively) are not required scientifically. Use of 424 (neurotoxicity in rodents) would be expected to cause considerable stress to animals, and also the end point is included in other TGs.

The OECD regards 428 (skin absorption: *in vitro* method) as being a full replacement for 427 (the *in vivo* method for skin absorption) (tab. 1), thus a TG for this endpoint *in vivo* is not needed. As the OECD views 432 as a complete replacement method, an *in vivo* phototoxicity protocol is also unnecessary.

TGs needing updating

Five TGs are clearly in urgent need of revision, four of which were originally adopted in 1981 and the remaining one in 1984, with none having been updated in the intervening period (tab. 2).



Apart from basic animal welfare issues, such as group housing and environmental enrichment, more worrying is the fact that these TGs ignore substantial advances made to the collection and analysis of information, and in the use of humane endpoints. This is particularly the case for 417 and 451 (toxicokinetics and carcinogenicity, respectively). Such techniques include non-invasive imaging (Hudson, 2005), better histopathology (Chejfee, 1999), humane endpoints (Combes et al., 2002) and biomarkers (Bottrill, 1998) (tab. 3).

The OECD lists 15 updated TGs (Anon., 2005a). However, the number of updated TGs is in reality less than the total listed (tab. 4). Thus, for 408, 409, 416, 418 and 419 no details of revisions are given, except for a year. Moreover, 420, 423 and 425 similarly have years for revision, but all supersede 401 (Botham, 2002), and not previous respective guidelines. Revisions of seven TGs do involve increased implementation of reduction and refinement (tab. 4), however.

Tab. 1: An analysis of the OECD *in vitro* test guidelines relevant to REACH

TG	Title	OECD notes	Comments
428	Skin absorption: <i>in vitro</i> method	Full replacement for TG 427 (<i>in vivo</i> method)	Therefore, TG 427 should be deleted
430	<i>In vitro</i> skin corrosion: TER	Replacement for corrosion part of TG 404	Therefore, TG 404 needs updating
431	<i>In vitro</i> skin corrosion: human skin model test	Ditto	Ditto
432	<i>In vitro</i> 3T3 NRU phototoxicity test	Full replacement (no existing TG)	Therefore, no need to develop an <i>in vivo</i> TG
435	<i>In vitro</i> skin corrosivity	Replacement for corrosion part of TG 404 for acids and bases only	Therefore, TG 404 needs updating; is there a need for both TGs 430 and 435?

Tab. 2: Some OECD Health Effects Test Guidelines that need updating

TG number (date)	Title	Comments
412 (1981)	Repeated dose inhalation toxicity: 28d or 14d study	Stressful procedures could be minimised by preliminary dose range finding study; blood collection before dosing should be avoided; dosing regimen, tissue retention and analysis could all be improved, effects of head only exposures on eyes needed (ophthalmoscopy)
417 (1984)	Toxicokinetics	Methods should involve: modern technology; guidance on housing and re-use of animals; prior hepatocyte screening for species selection; guidance on the need for PBPK modelling and full ADME information:
451 (1981)	Carcinogenicity studies	Revision to take account of new technical developments for tumour identification and characterisation; humane endpoints (including non-invasive imaging), timing of studies; observation of animals
452 (1981)	Chronic toxicity	Revision to clarify: group sizes; need for test when 90d study done; dosing regimens and routes; specific justification for second species
453 (1981)	Combined chronic toxicity/carcinogenicity studies	Revision required to address: why chronic element only applies to high dose and control groups; mode of administration and dosing regimens; use of dietary restriction; number of species

Tab. 3: Some modern techniques that could potentially improve the OECD Health Effects Test Guidelines both scientifically and with respect to animal welfare

Type of technique	Methods available
Molecular biomarkers	Toxicogenomics; proteomics; metabonomics
Non-invasive imaging/labelling	Bioluminescence; fluorescent markers; quantum dots; PET imaging; MRI scanning; ECG ventral plane videography (e.g. for early i.d. of tumours)
Body fluid analysis	AMS (accelerated mass spectrometry); NMR spectroscopy; PET imaging; identification of macromolecular adducts
Refined procedures (to facilitate compound administration; blood collection; measurement of blood pressure, heart rate)	Indwelling intravenous catheters; implanted vascular access ports; implanted telemetry devices
Refined procedures relating to pathological examination	Non-terminal and minimally invasive methods for obtaining body fluid and tissue samples – e.g. metabolic cages where excreta can be collected for analysis; immuno-histochemical analysis; confocal microscopy; fluorescence in situ hybridisation (FISH); PCR; PAGE; detection of apoptotic cells; differential screening of phage displayed libraries to identify cell surface markers



Integrating the use of the OECD TGs with non-animal methods

Some of the above improvements (tab. 4) have been achieved by using the TGs in a tiered testing strategy with *in vitro* assays. Combes et al. (2004) proposed the use of 11 non-animal methods with the OECD TGs in an integrated testing approach for REACH, such that the more animal-intensive TGs would not have to be used in many cases where positive data were obtained in earlier tests (tab. 6 in Combes et al., 2004; fig. 1; Combes et al., 2003; Combes et al., 2004; Grindon et al., 2005).

The above 11 methods are either awaiting formal validation (e.g. (Q)SAR, expert system and PBPK modelling and the SHE cell transformation assay), or are being validated (e.g. the use of basal cell cytotoxicity to predict acute toxicity), or have been validated (e.g. screens for eye irritation and embryotoxicity) (Spielmann and Liebsch, 2002).

The need for the OECD to focus more on updating TGs

The current levels of revision

The OECD has revised several TGs to reduce group sizes, change dosing regimes, and obtain more information from each animal (tab. 2 and 4). However, often technical changes to endpoint scoring have lagged behind new technologies.

Since 1981, 41 new guidelines have been adopted, one of which has been deleted, and 16 have allegedly been updated, although 8 of these were not true updates (tab. 5). This implies that the OECD places more emphasis on producing new TGs than on revising or deleting TGs.

The OECD system for producing new TGs

The OECD has schemes for: a) defining the need for a TG; and b) producing new TGs (Koeter and Visser, 2000). Neither of

Tab. 4: OECD analysis of Health Effects Test Guidelines (animal tests) relevant to REACH that have been updated/deleted

TG number	Title	OECD notes on date & details of updating	Comments
401	Acute oral toxicity	Date of deletion: 20 Dec. 2002	Other TGs rely on death as an endpoint
402	Acute dermal toxicity	24 Feb. 1987; reduction compared to original TG, lowering of dose level	
404	Acute dermal irritation/corrosion	24 April 2002; refinement/reduction – part of tiered testing strategy with <i>in vitro</i> screens	Corrosivity part should not be required as replacement test available (TG 430)
405	Acute eye irritation/corrosion	Ditto	Ditto
406	Skin sensitisation	17 July 1992; reduction method – by 50% compared to original TG	Should be deleted or guidance produced for its use only when LLNA unsuitable
407	Repeated dose 28d oral toxicity in rodents	27 July 1995; refined guideline with more information on: best dosing practice and from each animal	
408	Repeated dose 90d oral toxicity in rodents	21 Sept. 1998; animal test	Details of the updating not presented
409	Repeated dose 28d dermal toxicity in rodents	Ditto	Ditto
414	Prenatal developmental toxicity	22 Jan. 2001; reduction of 20% in number of animals used and more information from same animal	
416	Two generation reproductive toxicity	22 Jan. 2001; animal test	Details of the updating not presented
418	Delayed neurotoxicity of organophosphorus substances following acute exposure	27 July 1995; animal test	Ditto
419	Delayed neurotoxicity of organophosphorus substances; 28d repeated dose	Ditto	Ditto
420	Acute oral toxicity Fixed Dose Procedure	17 Dec. 2001; reduction and refinement of TG 401 (less suffering; smaller number of animals)	Not an update of the TG 420, but of 401
423	Acute oral toxicity – Acute Toxic Class method	Ditto; much smaller number of animals (10% of TG 401)	Ditto; still relies on death as endpoint
425	Acute oral toxicity – Up and down method	Ditto; provides a closer estimate of LD ₅₀ than TGs 420 and 423	Ditto; still relies on death as endpoint

these schemes includes any overt mention of specific mechanisms for updating or deleting TGs, although this is probably done via the existing system. A formal mechanism would, however, encourage the OECD to pay more attention to the need for these processes.

TGs for animal testing methods have traditionally become established and 'validated' following many years of use. Then, in the 1980s, several genotoxicity assays were validated by different interlaboratory validation studies before the protocols became OECD TGs. However, more recently, several refined *in vivo* and *in vitro* TGs have been produced following more stringent validation studies and peer reviews, according to internationally-agreed criteria, involving also the OECD (OECD, 2003; NIH, 1997; Combes, 2003).

The current focus of the OECD on producing new TGs

There are inconsistencies in the approach that the OECD has for developing TGs. Thus, it plans to introduce eight new TGs (tab. 6) under different circumstances. TG numbers have been assigned to, and drafts written for, TGs for inhalation and dermal exposure by using the Fixed Dose Procedure (FDP) and one for *in vivo* skin absorption test); all when there have apparently been no formal independent and totally transparent validation studies and peer reviews. A validation study of the FDP tests could probably be achieved by a retrospective weight of evidence review (Balls and Combes, 2005a). This is because the FDP for acute oral toxicity has been validated, although it took many years for a TG to be written (Combes et al., 2002). The *in vitro* micronucleus assay has been assigned a TG number and a

draft guideline has been produced (OECD, 2004), following interlaboratory studies (Kirsch-Volders, 1997). It is being validated retrospectively by ECVAM, then peer reviewed by the ESAC.

Some other test methods, either not validated or lacking a peer review report, are also being considered for TG development, e.g. the uterotrophic assay, the validation study of which was flawed (Combes, 2003), and the peer-review of which was not independent (Combes, 2004c), the OECD is even proceeding to draft a TG without a final published peer-review. Also, detailed review papers (DRPs) for the use of transgenic mice in carcinogenicity testing and the SHE cell transformation assay are being written, as a prelude to TGs, the former despite the failure of an interlaboratory study (van Zeller and Combes, 1999; Committee on Carcinogenicity, 2002).

Clearly, several of these tests are unnecessary or unready for conversion into TGs, and reflect the OECD's over-emphasis on guideline production. Several regulatory authorities are also prematurely accepting these methods (tab. 6), which is scientifically unjustified and could result in unreliable hazard data being produced.

Discussion

Strategies for test development, validation, peer review, TG production and adoption and regulatory acceptance are clearly inconsistent and require overhaul (as shown in fig. 2). The original approach (scheme 1; fig. 2) was developed when *in vivo*

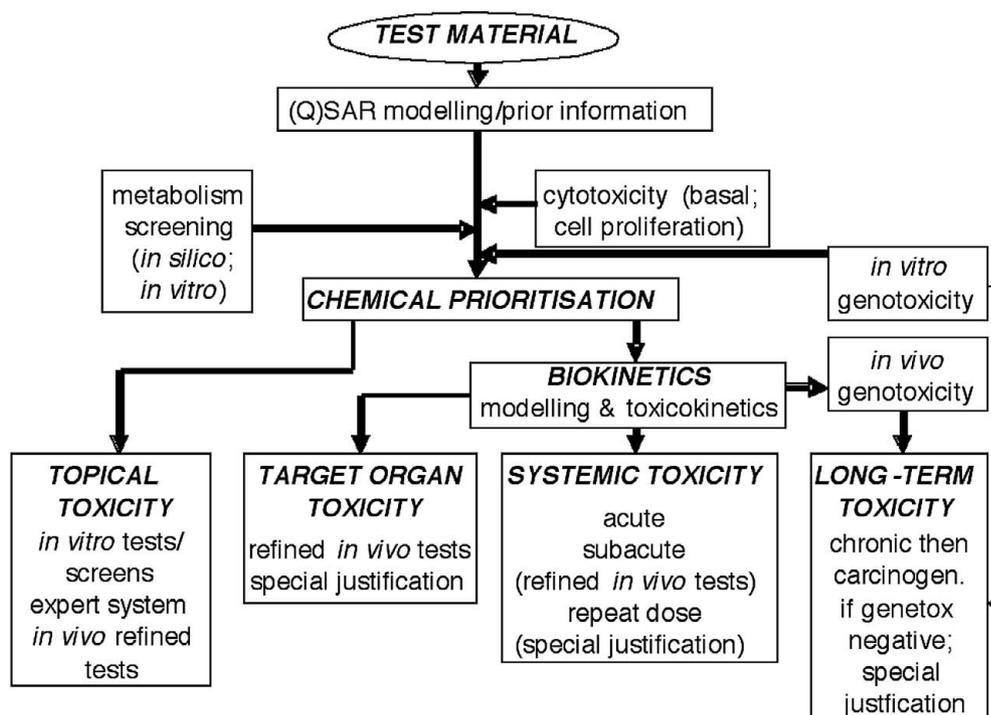


Fig. 1: Scheme for using non-animal and animal methods, including OECD Test Guidelines, in an integrated testing scheme for REACH (modified from Combes et al., 2004).

**Tab. 5: OECD analysis of Health Effects Test Guidelines (animal tests) relevant to REACH**

Date originally adopted/updated/deleted	Test Guidelines	Total number
1981	401, 402, 403, 404, 405, 406, 407, 408, 409, 410, 411, 412, 413, 414, 451, 452, 453	17
1983	415, 416	2
1984	417, 418, 419, 478	4
1986	484, 485	2
1987	401, 402, 406	1 (2)
1992	404, 420	1 (1)
1995	407, 418, 419, 421, Acute dermal photo-irritation screening (draft), 422	3 (3)
1996	403, 423	1 (1)
1997	424, 474, 475, 483, 486	5
1998	408, 409, 425	1 (2)
2000	426 (draft new)	1
2001	414, 416, 402E, 423E, 425E, 427 (draft)	1 (5)
2002	401, 404E, 405E, 429E	1 (2) (1)
2004	427	1
Totals		41 (16) (1)

updated tests*, deleted tests

*8 of these are unspecified or not true updates of the respective TGs

Tab. 6: Some test methods recently considered by the OECD for test guideline development.

Test	Status*					
	DRP	Validation study completed	Peer review endorsement	Draft TG	Regulatory approval	Notes
TG 433 FDP inhalation	Y	N	N	Y	N	No formal validation study, but method assessed by experts
TG 434 FDP dermal	Y?	N	N	Y	N	Ditto
TG 435 <i>in vitro</i> corrosivity	Y?	Y	Y	Y	Y	Specific for acids and bases
TG 427 <i>in vitro</i> skin absorption	?	N	N	Y	N	Limited scientific review; no scientific justification for TG
<i>In vitro</i> micronucleus	?	(Y)	N	Y TG487?	(Y)	Several small validation studies, results being subjected to a weight of evidence validation by ECVAM; ESAC to peer-review validation; OECD issued draft TG on 14.06.04; UK HSE accepts data
SHE cell transformation assay	Y	N	N	N	(Y)	ECVAM planning validation study; FDA accepts data to clarify other information
Uterotrophic assay	(Y)	Y	(Y)	(Y)	(N)	Published paper serves as DRP; peer review organised by OECD, but final report not been published; OECD proceeding with draft TG; Japanese authorities already accepting data from test
Transgenic mouse carcinogenicity assays	(Y)	(Y)	N	N	(Y)	DRP in preparation, based on unsuccessful ILSI validation; FDA encourages/accepts data from assays.

* parentheses indicate that answer is qualified

methods were never formally validated. Later, some tests, primarily those intended as non-animal replacements, or refinements of tests, underwent intensive validations and peer reviews before TGs production (scheme II; fig. 2). In contrast, other tests have not been properly validated and peer reviewed, yet have, or will have, TGs (scheme III; fig. 2). Also, premature regulatory acceptance has occurred (scheme IV; fig. 2)! A combination of all schemes (fig. 2) is in use in what seems to be an arbitrary way, probably as some consider *in vivo* tests to be inherently the most reliable, being based on intact animals, a scientifically absurd generalisation (Balls, 2004). Adoption of scheme II (Fig 2) would avoid premature TG development and regulatory acceptance.

The OECD is evaluating its Test Guidelines programme, and released an issues paper on 16 March, 2005 (Wagner, 2005; "Refocus of the Test Guidelines Programme") for discussion at the NCs meeting the following month. The paper, referring to Combes et al. (2004), stated: "*Updating these test Guidelines could be approached in different ways. Refinements and improvements could be made 'within' the test, to ensure that the test parameters and protocols reflected current science and regulatory requirementsor there could be improvement and enhancement 'across' tests, where test methods are modified and improved on the understanding of the role that the method plays in testing.*" However, unfortunately at the meeting (Anon., 2005b) updating of the TGs programme as a whole was apparently not discussed.

The need to validate revised TGs before their adoption should be considered case by case, and should utilise weight of evidence review as far as possible. A requirement for practical validation should not, however, detract from having the most modern TGs available.

Conclusions and recommendations

The OECD TGs programme is unsatisfactory; lacking a formal system for revising and deleting TGs, and needs overhaul. The OECD should just produce, update and delete redundant and obsolete TGs, instead of validating tests and producing guidance on validation (OECD, 2003) that it does not follow itself. The TGs might then become state of the art methods and more suitable for REACH.

Other bodies, like ECVAM, ICCVAM and JECVAM, should manage validation studies. No TG should be prepared, and no test accepted by a regulatory body, before satisfactory validation and peer review. If these processes are unsatisfactory the test should be considered for invalidation (Balls and Combes, 2005b).

Hopefully, the OECD will have the foresight to grasp this opportunity to revise the Test Guidelines Programme in a way that brings about these necessary changes.

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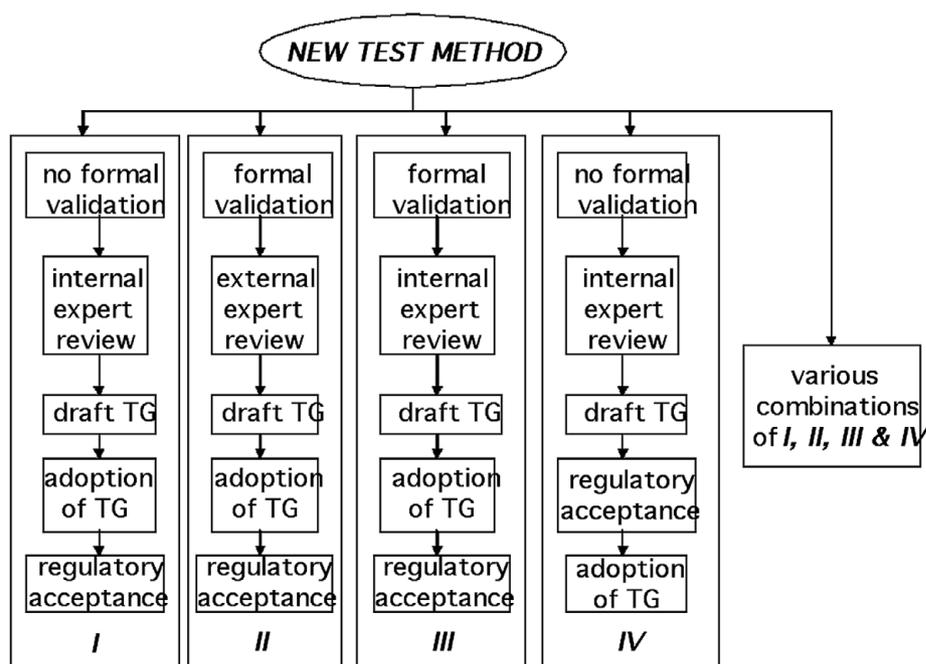


Fig. 2: A summary of the various schemes for the development and adoption of OECD Test Guidelines and regulatory acceptance.



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Challenges and Opportunities of Animal Welfare Organisations in Influencing and Making Public Policy

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Summary

For ethical and scientific reasons, the German Animal Welfare Federation strives for an end to all animal experiments. Amongst other issues, its political activities lately have been dedicated campaigns to end the use of non-human primates in research and on the new EU Chemicals Policy, REACH. Animal welfare requests are backed up by strong societal support. In influencing public policy animal welfare issues have to be weighed against other societal concerns, such as human health and environmental protection, and personal or economic interests. From the point of view of animal welfare, animal experimentation can be stopped without impeding human health or environmental protection.

Keywords: animal welfare, political activities, social values, non-human primate research, ethical evaluation, EU chemicals policy, REACH, non-animal testing strategies, animal testing ban

Introduction

According to Thomas Dye (2001), public policy is “whatever governments choose to do or not do.” As Schiffelers et al. (2005) note, a large part of the political activities of governments is aimed at preparing and implementing legislation: “The development of legislation in the EU is a complex process in which many institutions, actors and (formal and informal) rules play a role. By far the largest part of EU policy – and this applies to animal testing as well – eventually manifests itself in European law (regulations and directives). Within this formal, institutional framework, various actors use all kinds of influence and pressure with the aim of obtaining the desired legislative results. At the European level, lobbying is part and parcel of the legislative process. In many cases, consultation with special interest groups is a fixture in the formulation of policy.”

In the process of influencing and making public policy, animal welfare organisations see it as their role to speak up for the welfare of the individual animal. In accordance with Council Directive 86/609/EEC on the protection of laboratory animals (Commission of the European Communities, 1986), an “*experimental animal*” is being used for a scientific procedure, “*which may cause it pain, suffering, distress or lasting harm*”. Therefore the final goal in striving to protect these animals can only be the total abolition or replacement of such experimentation.

At the same time, animal welfare organisations acknowledge the contribution that reduction and refinement methods, the other two Rs of the so-called 3Rs principle (Russell and Burch, 1959), make in improving the welfare of laboratory animals.

Reduction implies that the new methodology uses fewer laboratory animals to pursue the same goal as before, whereas refinement means that the distress of the animals in a given procedure is reduced by changing the methodology. From the point of view of animal welfare such improvements are to be welcomed, however they can only be considered interim achievements.

Animal welfare organisations are backed up by strong societal support. The EU citizens’ concern about the welfare of animals is also reflected in the fact that animal welfare has been included in the Constitutional Treaty (Anon, 2004). Article III-121 reads: “*In formulating and implementing the Union’s ... policies, the Union and the Member States shall pay full regard to the welfare requirements of animals, as sentient beings...*”. A European survey from June 2005 on “Social values, Science and Technology”¹ came to the conclusion: “*82% of EU citizens uphold our duty to protect the rights of animals whatever the cost... in twenty-seven of the surveyed countries at least three in four share this point-of-view.*”

While animal welfare organisations engage in political activities to improve the welfare of animals, other stakeholders representing for example the scientific community, industry or environmental and consumer protection organisations, also put forward their requests. Thus, when advocating in favour of animal welfare issues, the following considerations have to be taken into account: Do animal welfare issues compete with the issues of human health and environmental protection? Do animal welfare issues compete with other issues, such as economic or personal interests?

These questions can only be answered on a case by case basis. In order to determine the significance and the true implications of any argument, either put forward against or in favour of animal testing, the underlying intention should be revealed and the scientific evidence brought forward to back it up should be evaluated. Again and again it can be shown that not only ethical, but

¹ Special Eurobarometer 225: Social values, Science and Technology, June 2005; http://europa.eu.int/comm/public_opinion/archives/eb/eb_225_report_en.pdf



also scientific reasons speak against animal experiments and that turning to non-animal test methods does not impede human health or environmental protection.

In the following, two examples are presented to show which challenges and opportunities animal welfare organisation face when striving for an end to animal experimentation: The campaign to ban research with non-human primates and the campaign to prevent animal testing under the new EU-Chemicals Policy.

Campaign to end research with non-human primates

While animal welfare organisations strive for an end to all experimentation with sentient animals, research with non-human primates always has been in the focus of their attention. Since these animal species are man's next of kin in the animal kingdom, using them in procedures that would be considered unacceptable in humans inevitably leads to an ethical conflict that cannot be disregarded. Every year, approximately 10,000 non-human primates are being used for experimental purposes in the European Union, and a reduction of this number is not discernible. Non-human primates are being used in fundamental research, for example in neurological or immunological studies, in an attempt to use an animal species that is as closely related to human beings as possible. For this same reason they are also being used in applied research, such as in toxicokinetic or pharmacodynamic studies. In a scientific and ethical evaluation of experiments with non-human primates, Ruhdel and Sauer (1998) revealed that the animals not only suffer from the procedures, but also due to acquisition and housing, whereas outstanding medical benefits that would justify the use of these animals could not be identified. From the point of view of animal welfare, there are compelling ethical reasons to discontinue experiments with non-human primates, while a multitude of adequate non-animal test methods are available to pursue the scientific questions currently addressed in experiments with these animals (Ruhdel and Sauer, 1998).

The European Commission has acknowledged the special concern related to the use of non-human primates in research. In the Preamble to Council Decision 1999/575 (Commission of the European Communities, 1999), in which the European Convention ETS 123 for the protection of laboratory animals (Council of Europe, 1986) was approved, it is stated: "*Whereas the use of primates for experimental and other scientific purposes carries the risk of suffering for those animals and therefore has to be reduced; whereas the use of primates for experimental and other scientific purposes has led to the catching of primates in the wild, and whereas, this should be avoided whenever possible in view of the suffering and losses which can arise during catching and transport.*"

² http://www.europa.eu.int/comm/environment/chemicals/lab_animals/

³ http://www.coe.int/T/E/Legal_affairs/Legal_co-operation/

⁴ For technical reasons, the official vote on the revised Appendix A is still outstanding. It currently is scheduled for the beginning of 2006.

The European Commission also specifically mentions the special concern for non-human primates and their inadequate covering by the current Directive to justify the need for the up-coming revision of Council Directive 86/609 on the protection of laboratory animals: "*Nor is the use of animals with a higher degree of neurophysiological sensitivity specifically regulated, such as in the case of non-human primates.*"²

On the level of the Council of Europe, legal activities relating to the scientific use of non human primates recently took place in the context of the revision of Appendix A "*Guidelines for accommodation and care of animals*" of European Convention ETS 123 on the protection of laboratory animals (Council of Europe, 1986). After the Parties to the Convention launched this revision at the 3rd Multilateral Consultation in May 1997, species specific expert groups were formed to design species specific guidelines for the housing of research animals. These experts were nominated from the non-governmental organisations, which attend the meetings of the Parties as observers.³

A scientist from the German Animal Welfare Federation joined the Primate Expert Group as representative of the European umbrella organisation Eurogroup for Animal Welfare. Notwithstanding the request for a ban on all experiments with non-human primates, this engagement was considered relevant because of the great suffering these animals endure under standard housing conditions. The current minimum standards, which continue to be the rule for the majority of non-human primates kept in European laboratories, are totally inadequate to enable these animals to fulfill even the most basic of their ethological needs, such to live in stable harmonious groups, to engage in meaningful activities and to perform a normal repertoire of species-specific locomotor activity. It is still legal to keep non-human primates singly in small barren cages, in which they cannot even move a few steps in one direction, let alone sit on a perch with their head upright and the tail hanging freely.

Nevertheless the negotiations surrounding the revision of guidelines for the accommodation of non-human primates turned out to be difficult. There was strong opposition against changing the still valid minimum standards at all. From the point of view of animal welfare there is no justification if animals that are being used and sacrificed for the alleged benefit of humans are not even housed in a way that they can fulfill their very basic species-specific needs. So-called "scientific" arguments also cannot be put forward to reject this: Housing non-human primates in enriched group enclosures does not stand in the way to regularly handling these animals, if trained adequately (Reinhardt, 2002). Clearly the reluctance to change cage dimensions is neither driven by the wish to improve human health or environmental protection, but by personal or financial interests.

It is to be welcomed that the Parties to the Convention supported the requests of animal welfare. The final draft guidance document approved by the Parties and published in the internet⁴ (Council of Europe, 2004) still is a compromise between economic and animal welfare issues, but it can make a considerable contribution to reducing the suffering of non-human primates due to inadequate housing conditions.

On the level of the European Union, animal welfare organisations will request a total ban on the use of non-human primates



for scientific purposes during the revision of Council Directive 86/609/EEC. In any case bans on the use of wild-caught non-human primates, on the genetic manipulation of non-human primates, and on procedures with medium or severe distress should be implemented as well as a ban on single housing of non-human primates except for limited duration on veterinary grounds.

EU chemicals policy campaign

In October 2003, the European Commission put forward the Draft REACH⁵ Regulation (Commission of the European Communities, 2003). The aim of this new EU Chemicals Policy system is better to protect humans and the environment from unwanted effects of chemicals, while at the same time taking into account economic issues.

Animal welfare organisations have given the new EU Chemicals Policy high priority for campaigning, because of its risk of leading to a huge increase in animal testing – up to 45 million additional animal tests according to official predictions (Höfer et al., 2004). This should be prevented, also in the sake of human health and environmental protection. The redesign of the entire area of chemicals legislation should be used as a chance for a paradigm change in favour of non-animal safety testing strategies.

In order to ensure that REACH will truly serve to improve safety protection, flexible testing strategies should be developed and implemented for all relevant endpoints that make use of significant, scientifically validated non-animal test methods instead of unreliable animal tests. Nevertheless not even all currently available non-animal test methods have been included in the Draft Regulation. Schiffelers et al. (2005) consider resistance from authorities to be one of the main reasons for such problems: “...any cost/benefit assessment usually favours an existing policy rather than a new one. New policy is often seen as a potential liability. This point is illustrated by a civil servant's comment on policy changes: ‘It's better not to change ten times, than to make nine changes for the better and one for the worse’...Still, the reluctance of policy-makers and decision-makers to incorporate alternatives seems to result from a combination of factors such as attitude, knowledge and risk acceptance.” From the point of view of animal welfare, it is totally unacceptable if non-animal test methods that have shown their scientific validity according to internationally agreed criteria – a procedure that the vast majority of animal tests never were submitted to – are not included in regulatory testing strategies.

Animal welfare organisations also request data sharing to become mandatory in the REACH Regulation. The majority of the chemicals that will be covered under REACH are existing

substances that have been in use for over 25 years. It is entirely impossible that there should be no data on their effects. They only never were reported to the authorities. Nevertheless, again and again representatives from industry speak up that they would prefer to pay a fee in order to be able to keep data to themselves. From the point of view of animal welfare such requests are unacceptable. They do not serve human health or environmental protection and clearly stand in the way to preventing animal testing.

All in all, in the future EU Chemicals Policy, full consideration of animal welfare issues is the key to ensure that the goals to improve human health and environmental protection can be met and they do take into account economic issues. However, to reach these goals, substantial amendments to the Draft REACH Regulation remain indispensable.

The EU legislative procedure is complex with a multitude of key players. The European Parliament and the Council are main key players since they have co-decision power on finalising the REACH Regulation. In the EU Parliament, legislative work is prepared in the Committees. Concerning REACH, the Environmental Committee has taken the lead, with Industry and Internal Market Committees also putting forward proposals for amendment and the Committees for Legal Affairs, Employment, Women's Rights, Economy, Budget and International Trade giving their opinions. The final proposals for amendment are adopted in the plenary of the Parliament.

In parallel the Draft REACH regulation is dealt with in the Environment and Competitiveness Councils. Preparatory work for the Council meetings is accomplished on the level of the Committees of Permanent Representatives, who formed Ad hoc Working Groups for this task.

The Council being formed by the Ministers of the Member States governments, its position is influenced by opinions formed on the national levels. The German Government, for instance, must take into account comments from the Upper and the Lower Chambers⁶ and receives advice from three different authorities, the German Federal Institute for Risk Assessment (BfR⁷), the German Environmental Protection Agency (UBA⁸) and the Federal Institute for Occupational Safety and Health (BAuA⁹).

In influencing the development of the new Chemicals Policy, the work load of addressing all these key players is distributed between national animal welfare organisations and their European umbrella organisations, Eurogroup for Animal Welfare¹⁰ and the European Coalition to End Animal Experiments.¹¹

Conclusions

What would be the consequences of stopping animal testing as requested by animal welfare organisations in their engagements to influence public policy? Animal experiments are merely one type of test method amongst a multitude of others, and often-times scientific arguments can be put forward to show that they are unreliable or misleading. Research without animals seems possible, provided that scientists and politicians are willing to

⁵ REACH – Registration, Evaluation, Authorisation of Chemicals

⁶ Bundesrat, Bundestag

⁷ BfR – Bundesinstitut für Risikobewertung

⁸ UBA - Umweltbundesamt

⁹ BAuA – Bundesanstalt für Arbeitsschutz und Arbeitsmedizin

¹⁰ www.eurogroupforanimalwelfare.org

¹¹ www.eceae.org



change their attitudes, to develop new ways of thinking and to pursue new research strategies, by asking new scientific questions. As long as animal experiments are being performed, it is inevitable to address the question whether everything should be considered acceptable that is feasible. In pursuing the goal to prevent animal testing, solutions can be found that are compatible with other societal interests, such as improving human health and environmental protection. However, from the point of view of animal welfare, economic issues and personal interests should not be allowed to override animal welfare issues.

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