ANIMAL TESTING REVIEW PANEL

REPORT FOR 2013

INTRODUCTION

Shell seeks to implement the 3Rs of animal testing (replace, reduce, refine) wherever possible while meeting legal obligations and protecting human life and the environment. Any Shell-owned or Shell-operated company must follow Shell animal testing standards when laboratory-based toxicology experiments are conducted on animals, even in those countries that have less stringent requirements.

Each year the Animal Testing Review Panel ("the panel") examines and comments on the implementation of Shell animal testing requirements. This external panel works with Shell to ensure best practice in laboratories and advises on Shell external engagement to support the development and application of the 3Rs. The membership and terms of reference of the Animal Testing Review Panel are provided at the end of this report.

This document details Shell's ongoing efforts to replace, reduce and refine animal testing by progressing new and alternative testing methods and by increasing the use of *in vitro* assays. The report also describes Shell's external engagement and advocacy for the use of alternative methods, as well as its governance and control of animal testing activities. A breakdown of Shell use of animals in 2012, to assess the safety characteristics and environmental impact of Shell products, operations and manufacturing processes, is provided at the end of this report. This report has been reviewed and approved by the panel.

GOVERNANCE AND CONTROL OF ANIMAL TESTING ACTIVITIES

As part of its Business Principles, Shell commits to contribute to sustainable development. This requires integrating economic, environmental and societal considerations into decision making. Shell wants to be a responsible member of society, and addressing animal testing in a responsible way is part of this. Animal testing is governed under Shell Health, Safety, Security and the Environment (HSSE) risk control framework. The framework specifies clearly when Shell-owned and Shell-operated companies are to apply the 3Rs in product safety evaluations. The panel discussed the application of Shell of its animal testing requirements in the selection of contract research organisations for animal testing. These requirements focus on animal welfare and exceed legislative obligations.

The panel felt that the current level of governance of animal testing in Shell was appropriate. The panel offered their expertise to enhance the knowledge of Shell animal testing experts. The panel suggested that Shell continues to ensure that the contract research organisations it uses for animal testing have the correct level of staff competency required.

REPLACEMENT, REDUCTION AND REFINEMENT OF FISH TESTING

Shell does not use cats, dogs or monkeys in any of its tests. The majority of animal use by Shell is for the testing of fish to meet regulatory requirements. Shell makes in our opinion significant efforts to reduce fish testing and to develop alternative methods that may eventually replace it.

In 2012 Shell informed the panel that it had reduced fish testing by nearly 10%. Several Shell sites, which were required to conduct fish testing on a monthly or quarterly basis, lowered their testing frequency while still meeting local regulatory requirements.

Shell also updated the panel on the progress of a consortium research project carried out by the US Environmental Protection Agency, the International Life Sciences Institute - Health and Environmental Sciences Institute (ILSI-HESI), Shell and three other companies. The project was initiated in 2011 to assess the use of fish embryos from the zebra fish and fathead minnow as an alternative to chronic aquatic toxicity testing. The fathead minnow is used by the US National Pollutant Discharge Elimination System as a test-compliant species. Recent study results of this research project show that more work is needed to overcome some technical challenges in the alternative assay.

Although a number of fish were used to assess the suitability of the alternative assay, the work was done by a consortium to enable the test data to be shared. In order to avoid duplication of testing, Shell conducts as much testing as possible as part of consortia. Nevertheless, Shell reports animal use on a 100%-basis (ie, the total number of animals used by a consortium is reported). This means that the 'actual' reduction in animals used by Shell is not visible in our public reports.

The panel complimented Shell's initiative to reduce the frequency of mandatory fish testing. It noted that Shell performed as much testing as possible in consortia to avoid duplication and share data. This is a very efficient way to reduce overall animal use, as the alternative would be for each company to perform the same tests. The panel endorsed Shell's efforts to use alternatives to chronic aquatic toxicity testing.

ALTERNATIVES TO SCREENING-LEVEL ASSESSMENTS

The panel discussed Shell's efforts to develop a toolbox of alternative assays to fill important gaps in understanding the safety characteristics of petroleum products. In 2012 Shell developed a more robust quantitative structure-activity relationship (QSAR) model for acute fish eco-toxicity. This was achieved by leveraging the data submitted for REACH (the European Community regulation on the registration, evaluation, authorisation and restriction of chemical substances). It resulted in an improved predictability of the existing QSAR model. In addition, daphnia toxicity kits were modified and validated in-house to enable quantitative experimental data to be generated quickly. Future efforts will focus on developing a QSAR model for chronic fish eco-toxicity and on creating an alternative method for monitoring the toxicity and bioaccumulation potential of effluents.

Shell also enhanced its toxicology toolbox for evaluating endpoints that are relevant for human health. The toolbox uses QSAR models and *in vitro* techniques to assess skin and eye irritation and skin sensitisation. For skin sensitisation, materials were examined using a new OECD adverse outcome pathway decision tree scheme. Shell will continue to assess the use of this new decision tree for other regulatory applications. Our experience of it in 2012 provides in our opinion a valuable foundation for future assessments.

The panel noted that Shell's use of *in vitro* methods to test skin sensitisation using the adverse outcome pathway decision tree scheme is very timely. This is especially relevant because the US Food and Drug Administration (FDA) has indicated that the Interagency Coordinating Committee on the Validation of Alternative Methods – Local Lymph Node Assay (ICCVAM LLNA) test recommendations are not acceptable for satisfactorily fulfilling the test needs for FDA regulated products. Rather, the FDA would like to see a screening battery of *in vitro* assays.

SHELL'S EXTERNAL ENGAGEMENT IN ALTERNATIVE ANIMAL TESTING METHODS

Shell is active in a number of groups whose long-term aim is to develop humane and alternative means of evaluating the health and environmental effects of oil and chemical products. Shell's current external engagement includes:

- member of the Advisory Board of the Johns Hopkins Centre for Alternatives to Animal Testing (CAAT), providing guidance and direction to the research programmes that CAAT sponsors; participates in workshops and symposia, and is kept current with the developments of in vitro and humane science;
- participation in the European Chemical Industry Council's (Cefic) Long-Range Research Initiative, which coordinates industry efforts in support of the 3Rs;
- engagement with a joint European Commission-industry initiative, the European Partnership for Alternative Approaches to Animal Testing (EPAA), through Cefic;
- participation in the Regulatory Steering Group and in a task force for the development of alternative approaches to fish testing, and co-sponsor of the CRACK IT Challenge to develop a screening tool for reproductive toxicity at the UK National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs);
- membership of the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), which supports task forces and convenes workshops to advance the science necessary to replace animal testing;
- participation in an ILSI-HESI project and task force on animal alternative needs in environmental risk assessment; and
- participation by Shell scientists in forums and conferences on animal testing in Europe and North America.

The panel considers Shell's external engagement to be appropriate, given the importance of legal obligations and the need to protect human life and the environment.

IMPACT OF REACH ON SHELL USE OF ANIMALS

The first REACH registration deadline for high-hazard and high-volume substances was December 1, 2010.

Shell worked largely through industry consortia to meet this registration deadline. The extensive use of read-across, trend analysis, data sharing and toxicity-prediction models, as well as exposure-based waiving, allowed Shell and its consortia partners to propose waivers for most types of animal testing in the REACH dossiers they submitted. The European Chemicals Agency (ECHA) had in several instances challenged the use of categories, read-across methods and the use of computer models to estimate toxicity. Shell and its industry partners continue to engage with ECHA to address any concerns with REACH dossiers.

The feedback from ECHA on the dossiers submitted by consortia of which Shell was a member was that animal reprotoxicity testing was insufficient. Historically, animal reprotoxicity testing has not been required by regulatory authorities. Current REACH guidelines indicate that a two-generation reproductive toxicity test, OECD 416, meets REACH information guidelines. This test requires the use of about 2,400 animals. Considering the draft decisions received to-date and the final REACH dossier updates, the final testing proposed comprises mainly prenatal development studies and two-generation studies with an estimated total number of 50,500 animals involved (rodents). Alternative testing strategies were proposed but not accepted to fill data gaps.

Shell remains committed to the goals of REACH, both to demonstrate the safe use of chemicals and to reduce the use of animals in testing. The second REACH registration deadline was 31 May 2013. Shell has registered substances that are manufactured in or imported into the EU in amounts greater than 100 tonnes per year. Shell will continue to work with industry partners to minimise REACH testing whenever it is scientifically justified.

The panel was encouraged by Shell's advocating *in vitro* alternatives that support category approaches for REACH. The panel observed that although REACH legislation promotes alternatives, lack of acceptance of these alternatives by ECHA was disappointing. The panel highlighted opportunities to promote animal welfare with European regulatory authorities for the implementation of REACH.

WHAT SHELL REPORTS

In line with standard industry practices, Shell reports on the activities of Shell-owned and Shell-operated companies. Testing programmes that are supervised by industry consortia in which Shell participates are reported separately. Shell reports all experimental animal use on a 100%-basis (each animal is counted as Shell's even if the testing programme is undertaken by multiple companies). Testing data is collected from internal sources and from reports provided by external testing laboratories.

SHELL USE OF ANIMALS FOR TESTING IN 2012

Shell use of animals to assess the safety characteristics and environmental impact of its products, operations and manufacturing processes from 2008 to 2012 is reported in Table 1. Tests that Shell currently commissions use mainly laboratory-bred rats, mice and fish and do not involve cats, dogs or monkeys. Mandatory testing of fish to meet regulatory requirements made up 72% of all animal use by Shell-owned and Shell-operated companies in 2012.

TABLE 1: NUMBER OF LABORATORY ANIMALS USED, 2008-2012

Tests commissioned by	Animals used	Number of animals				
		2008	2009	2010	2011	2012
Shell	Rodents	592	64	2,501	2,497	150
Shell	Rabbits	6	21	9	6	9
Shell	Fish	54,986	43,093	38,524	33,753	30,832
Shell	Birds	0	0	0	90	0
Industry consortia	Rodents	2,009	3,194	4,411	748	7,944
Industry consortia	Rabbits	7	0	9	0	6
Industry consortia	Fish	0	0	271	0	4,368
Joint ventures	Rodents	0	0	0	0	0
Joint ventures	Rabbits	0	0	0	0	0
Joint ventures	Fish	1,280	7,388	4,190	11,763	4,180
Total		**58,880**	**53,760**	**49,915**	**48,857**	**47,489**

Notes: Industry consortia are groups of companies (including Shell) that co-operate, usually within the framework of an industry trade association, to share available data and the costs of testing programmes on particular chemicals or groups of chemicals. **Joint ventures** include companies where Shell is the operator and those companies under Shell control.

The use of mammalian species in 2012 is detailed in Table 2. Rats were used mainly to fulfil requirements for the US Environmental Protection Agency's High Production Volume Challenge (HPV Challenge) programme, specifically in four prenatal developmental toxicity studies. The HPV Challenge programme is a voluntary initiative by the industry to provide a standard data set, mainly based on tests using animals, for substances produced in excess of one million pounds in weight per annum. Mice were used to assess the modes by which certain substances exert toxic effects. Rabbits were used to assess skin and eye irritation end points to meet regulatory requirements in those countries where alternative tests were not accepted. Guinea pigs were used for the guinea pig maximisation test to fulfil regulatory requirements for a substance expected to cause a false positive result in the local lymph node assay. Syrian hamsters were used for the Syrian hamster embryo assay as an alternative method to investigate carcinogenic potential.

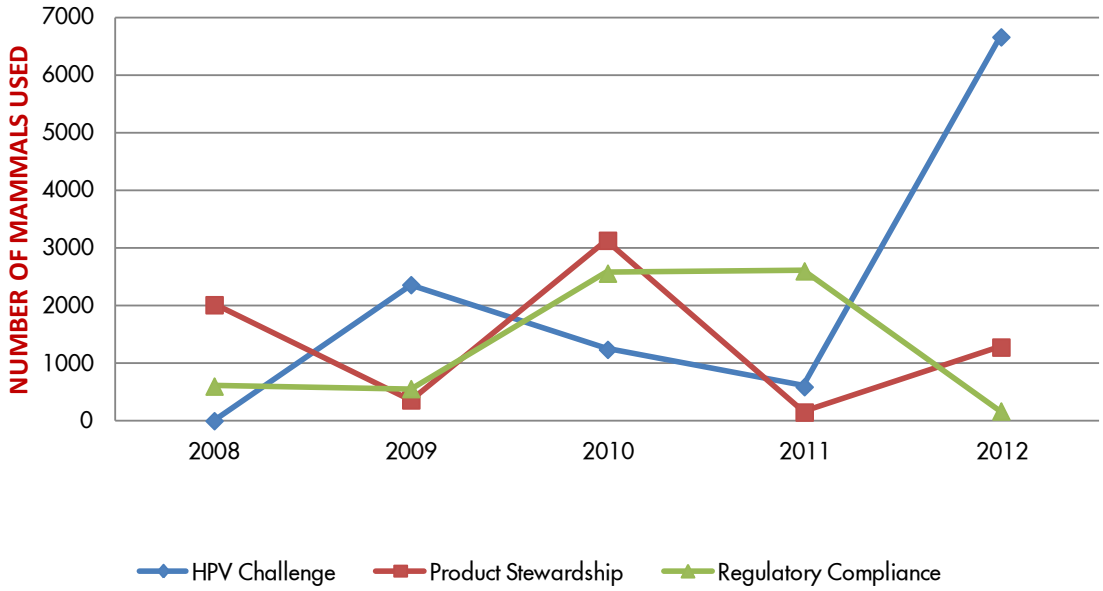
Shell used 8,109 mammals to assess product safety in 2012. Through application of the 3Rs, Shell avoided the use of 78 mammals. This was achieved primarily by lowering the number of studies in mode of action investigations, and by lowering the number of animals per dose group in sensitisation studies. While Shell constantly strives to reduce the numbers of animals used, Shell also has a responsibility to take into account the statistical viability of the numbers used in order to deliver defensible and reliable results. Where appropriate, Shell involves a biostatistician to ensure the data requirements are met whilst using the least number of animals.

TABLE 2: MAMMALIAN SPECIES USED IN 2012

Species	Number
Rats	6,843
Mice	1,172
Guinea pigs	15
Syrian hamsters	64
Rabbits	15
Total	**8,109**

The purpose of performing tests on mammalian species is illustrated in Figure 1. The figure shows the number of animals used in tests commissioned by Shell, by industry consortia and by Shell-operated joint ventures. In general, Shell expects that animal use is likely to increase in the near-term to meet the increasing requirements of the European Union's REACH regulation. The EU regulatory authorities review all testing proposals for studies required for REACH compliance before testing is conducted.

FIGURE 1: PURPOSE OF TESTING IN MAMMALIAN SPECIES



Notes: The US EPA High Production Volume Challenge (**HPV Challenge)** programme is a voluntary initiative by the industry to provide a standard data set, mainly based on tests using animals, for substances produced in excess of one million pounds in weight per annum. **Product stewardship:** Data is required to understand the health and environmental hazards of a product and is not collected for regulatory purposes. This may include generation of detailed information on the mechanism of toxic action. **Regulatory compliance:** Testing is required by law.

The use of fish from 2008-2012 is summarised in Table 3. Regulatory requirements in North America were the main reason for the use of fish. In 2011, the total number of fish increased due to an increased operational footprint in North America. In 2012 Shell demonstrated compliance with local standards, resulting in a reduction of the testing frequency enabling us to reduce the number of effluent tests in these operations. This is directly reflected in the fish use, which decreased significantly in 2012 compared to 2011.

Most of the fish used for product stewardship tests were in a project designed and managed by the Health and Environmental Sciences Institute (HESI) Animal Alternatives in Environmental Risk Assessment Project Committee. The project evaluated alternative strategies to assess the effects of effluent toxicity on fish. It investigated the relationship between existing alternative methods, such as the fish embryo toxicity test, and common sub-chronic methods such as the seven-day larval growth and survival assay.

Shell avoided the use of 157 fish by using a staged testing approach. In this approach substance classification is based on tests on algae and daphnia, or on reducing the number of range finders and applying limit-test procedures whenever they are scientifically justified and legally permitted.

TABLE 3: USE OF FISH, 2008-2012

Purpose of test	2008	2009	2010	2011	2012
HPV Challenge	0	0	72	0	0
Product stewardship	160	0	0	17	5,060
Regulatory compliance	56,106	50,481	42,913	45,029	34,320
Total	**56,266**	**50,481**	**42,985**	**45,516**	**39,380**

Notes: In addition to product safety testing, some countries (particularly the USA and Canada) required the use of fish to assess the toxicity of discharges into water and certain waste streams. Operating permits for industrial sites, such as oil refineries, chemical plants, supply and distribution terminals, and retail sites require the toxicity of effluent waters to be tested in a range of aquatic organisms, including fish. Table 3 also includes fish used in response to US regulatory requirements to estimate environmental hazards during site clean-up operations.

The panel was pleased that Shell actively intervened to reduce the number of fish used. It felt, however, that the reduction in numbers alone did not fully reflect Shell's efforts to promote animal welfare. The panel commended Shell for its transparency on animal use and judged the company's efforts to be a positive example for the industry as a whole. The panel noted that the increase in fish use by consortia was in fact a reduction in animal use, as the data were shared by the members of each consortium. The panel encouraged Shell to continue testing in consortia as this will result in an overall reduction in animal use.

CONCLUSION

The Animal Testing Review Panel has:

- critically reviewed Shell use of animals;
- reviewed and commented on Shell's efforts to promote the 3Rs;
- discussed the implications of REACH and the new EU animal welfare directive on Shell use of animals;
- encouraged Shell to continue testing in consortia to reduce overall animal use;
- reviewed Shell internal processes to control animal testing risks;
- discussed the role and level of overview by the panel; and
- complimented Shell for being a positive example of transparency in the area of animal testing.

ABOUT THE PANEL

In 2001, Shell formalised its practices on animal testing by creating a more structured management process and by better communicating its position internally and externally. An external Animal Testing Review Panel was established to provide independent scrutiny of and support for Shell's activities in this area.

TERMS OF REFERENCE OF THE PANEL

Individual panel members are invited by Shell to serve on the panel for a period of three years, with the possibility of being invited to serve for a second term of three more years. The panel recommends candidates who could be invited by Shell to join the panel, either as replacements for current members when their term is completed, or to supplement the current panel membership.

The panel meets twice a year with key Shell personnel. It does not verify the accuracy of the data underlying the report. Besides assessing Shell's reporting on animal testing, the panel offers observations and advice on the company's performance with respect to the 3Rs. In recognition of their time and expertise, panel members receive an honorarium and reimbursement of travel and accommodation expenses.

PANEL MEMBERSHIP IN 2013

Kees van Leeuwen (Principal Scientist, KWR Watercycle Research Institute and Professor of Water Management and Urban Development, Utrecht University, the Netherlands), Panel Chair
Kees van Leeuwen is currently a principal scientist at KWR Watercycle Research Institute and is involved in issues related to the risk assessment of chemicals, emerging compounds in the urban water cycle and sustainability of the urban water cycle. He was previously principal scientist at TNO (the Netherlands Organisation for Applied Scientific Research), Director of the Institute for Health and Consumer Protection for the European Commission, and Professor of Toxicology at the University of Utrecht. He has written numerous scientific articles and edited two editions of a book on the risk assessment of chemicals. He has a special interest in intelligent testing strategies.

Grahame Bulfield (Senior Honorary Professorial Fellow and Emeritus Professor of Genetics, University of Edinburgh, UK)
Grahame Bulfield spent the first 24 years of his career as a research geneticist. He was Chief Executive of the Roslin Institute from 1988-2002 where he transformed Roslin from a traditional farm-animal research institute to a leader in the application of modern biotechnology to animals. In 2002, he was appointed Vice-Principal of the University of Edinburgh and Head of its College of Science and Engineering. Since his retirement in 2008, he has been a non-executive director and a consultant in the life sciences sector. He has advised the UK government on animal testing and welfare issues.

Charles Gentry (independent consultant on laboratory animal science)
Charles Gentry is a company director with international expertise in laboratory animal science. He has a specialist interest in compliance with UK and EU legislation, and in the implementation of good practice. He is a former Director and Certificate Holder under A(SP)A 1986 at the

University of Cambridge, UK. Mr Gentry is Chairman of the Certificate Holders Forum UK, a member of the Fondazione Guido Bernardini Scientific Committee, and Chairman of the Lantra Advisory Group (UK) on laboratory animal science.

Alan Goldberg (Professor of Toxicology and Chairman of the Board, Center for Alternatives to Animal Testing, Johns Hopkins University, USA)
Alan Goldberg is a toxicologist focusing on *in vitro* toxicology and the use of *in vitro* data in risk assessment. As the Chairman of the Board for the Johns Hopkins Center for Alternatives to Animal Testing (CAAT), he is deeply committed to the 3Rs of humane science. He was a commissioner of and recently completed a study for the Pew Charitable Trusts on the impact of industrial farm animal production on public health, the environment, animal welfare and social justice. He has served on governmental and non-governmental boards dealing with laboratory animals.