ADVISORY PANEL ON ANIMAL WELFARE

REPORT FOR 2014

EXECUTIVE SUMMARY

Shell's long-term objective is to minimise the use of animal testing by making use of suitable alternative risk assessment methods, at the same time ensuring a high degree of human health and environmental protection. To achieve this objective, Shell is following an integrated strategy with five strands:

i) Using non-animal-based tests wherever suitable (example: employing in vitro skin and eye irritation tests and read-across strategies);
ii) Co-operating with other companies to share animal testing data (example: most Gas-to-Liquids (GTL) testing was performed together with other Integrated Oil Companies);
iii) Challenging regulatory authorities to make changes in their testing requirements to use live animals where suitable alternative tests are available (example: active involvement in read-across discussions with ECHA);
iv) Playing a lead role in developing and promoting alternative tests (example: our involvement in the NC3Rs organisation);
v) Where mandatory tests cannot be avoided, ensuring that these are conducted using accepted regulatory guidelines.

One particular barrier to progress has been a reluctance by regulatory authorities to accept alternative methods and/or a read-across strategies. Our priority for the coming year is to: 1) support research and development of alternative methods; 2) continue to advocate and lobby policy makers to accept non-animal methods; and 3) to work through consortia to minimise the numbers of animals used in mandated testing.

INTRODUCTION

Shell implements 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.

Every year the external Advisory Panel on Animal Welfare ("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. It also advises on Shell's external engagement supporting the development and application of the 3Rs. The membership and terms of reference of the external Advisory Panel on Animal Welfare 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 2013 breakdown of Shell's use of animals to assess the safety characteristics and environmental impact of its 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 aims to be a responsible member of society, which includes addressing animal testing in a responsible way. Animal testing is governed under the Shell Health, Safety, Security and 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's animal testing requirements in the selection of contract research organisations for animal testing. These requirements focus on animal welfare and exceed legislative obligations.

REPLACEMENT, REDUCTION AND REFINEMENT OF TESTING

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

Shell 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 testing treated wastewater effluents for chronic aquatic toxicity. The fathead minnow is used by the US National Pollutant Discharge Elimination System as a test-compliant species. At the time of publication, we note that more work will be needed to overcome remaining some technical challenges in developing the alternative assay, and the scientific team is developing a research plan to continue the work.

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

Another successful technique for limiting the use of animals is the application of quantitative structural activity relationships (QSAR) using physical and chemical property data backed up with a limited animal test database to predict chemical toxicity. QSAR are being used to predict toxicity of complex mixtures across a range of compositions, instead of generating these toxicity data by animal 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 2013 Shell developed a more robust quantitative structure-activity relationship (QSAR) model for chronic 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 and was published in a scientific journal and presented at the Society of Environmental Toxicology and Chemistry (SETAC) conference in Europe. 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 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 2013 provides, in our opinion, a valuable foundation for future assessments and dialogue with regulatory agencies and the scientific community.

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:

- membership 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; Shell participates in workshops and symposia, to be 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 co-ordinates 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 BUSINESS CLIMATE AND ANIMAL TESTING

Shell maintains its licence to operate and expand into new business by complying with all applicable regulations. For example, as in the past few years, Shell will continue to grow its sustainable Gas-to-Liquids (GTL) business. In doing so, it will be required to register products in many different countries which will have their own requirements for animal testing. Although we

advocate read-across between the various GTL products as much as possible, and optimise the testing design to comply with the various regulations world-wide, conducting some specific tests as required by regulatory authorities is unavoidable. Similarly, as Shell moves for water conservation and strives to return process-treated waters in our Canadian heavy oil facilities, government requirements for animal testing to assure compliance with environmental standards will be in force.

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.

ECHA commented on several submitted dossiers that animal reproductive toxicity testing was inadequate. To avoid extensive testing alternative testing strategies were proposed although not currently accepted.

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. Shell will continue to work with industry partners to minimise REACH testing whenever it is scientifically justified.

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 2013

Shell use of animals to assess the safety characteristics and environmental impact of its products, operations and manufacturing processes from 2009 to 2013 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 69% of all animal use by Shell-owned and Shell-operated companies in 2013.

TABLE 1: NUMBER OF LABORATORY ANIMALS USED, 2009-2013

Tests commissioned by	Animals used	Number of animals				
		2009	2010	2011	2012	2013
Shell	Rodents	64	2,501	2,497	150	4,368 (4,350)*
Shell	Rabbits	21	9	6	9	870 (870)*
Shell	Fish	43,093	38,524	33,753	30,832	44,696 (3,045)*
Shell	Birds	0	0	90	0	0
Industry consortia	Rodents	3,194	4,411	748	7,944	5,763
Industry consortia	Rabbits	0	9	0	6	4
Industry consortia	Fish	0	271	0	4,368	5,576
Joint ventures	Rodents	0	0	0	0	0
Joint ventures	Rabbits	0	0	0	0	0
Joint ventures	Fish	7,388	4,190	11,763	4,180	10,020
Total		**53,760**	**49,915**	**48,857**	**47,489**	**71,297**

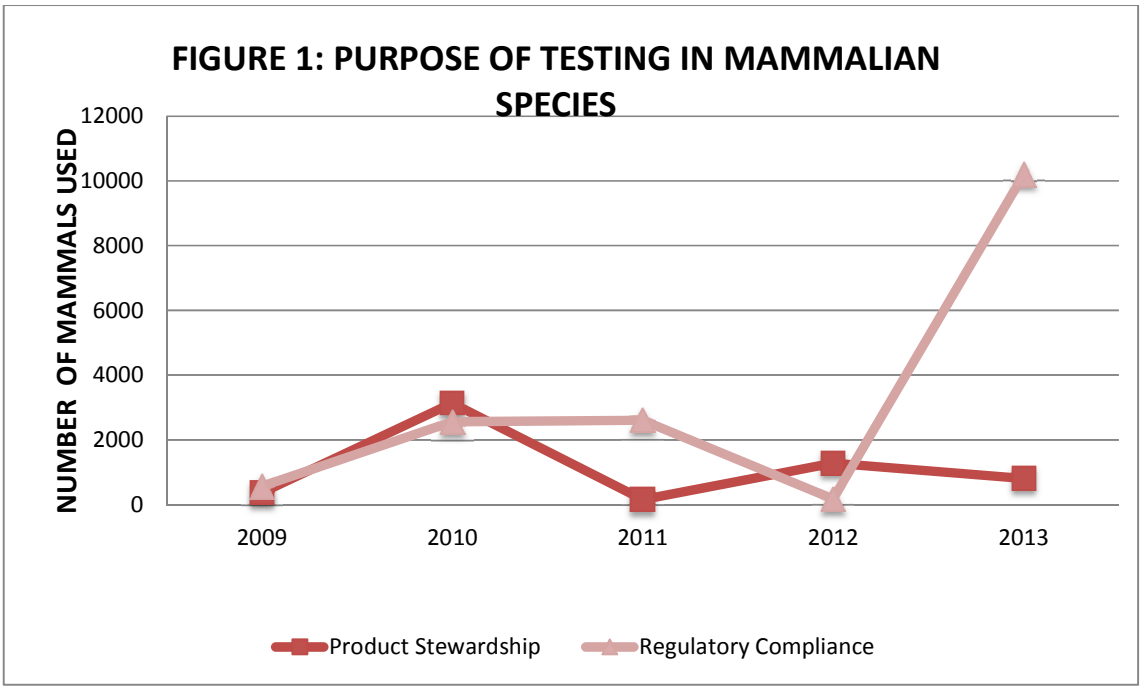
Notes: Industry consortia are groups of companies (including Shell) that co-operate, usually within the framework of an industry trade association, to share available data and the costs of testing programmes on particular chemicals or groups of chemicals. **Joint ventures** include companies where Shell is the operator and those companies under Shell control. * The numbers in brackets represent the numbers of animals that are used in the product testing, which was carried out as a requirement by Chinese authorities.

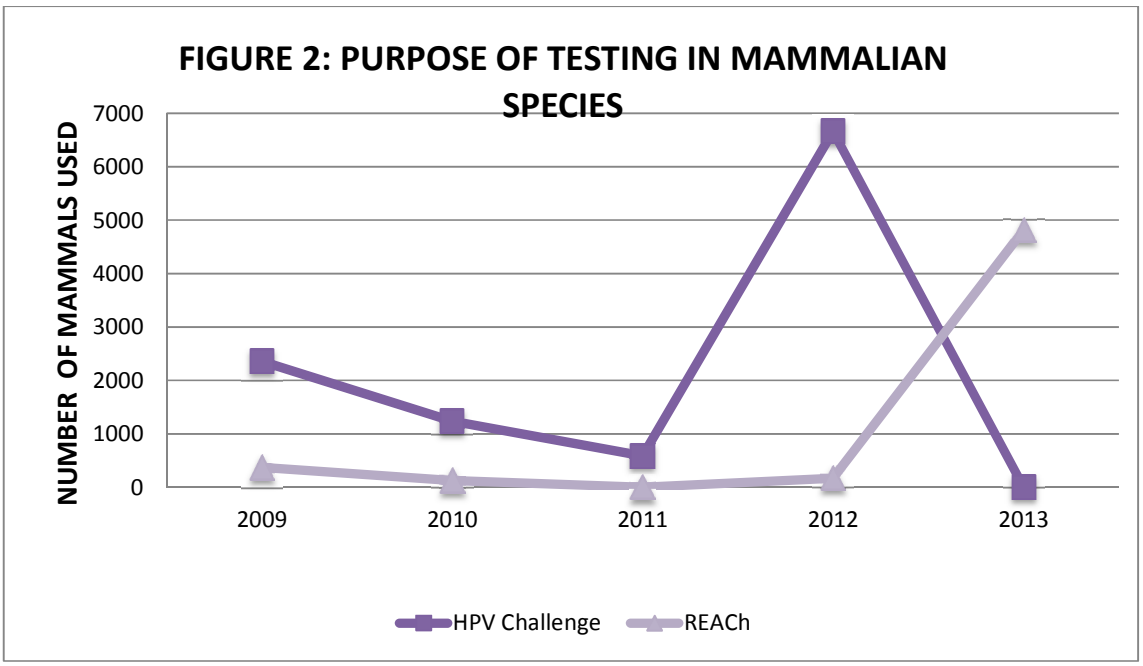
The use of mammalian species in 2013 is detailed in Table 2. Rats were used mainly in industry consortia for regulatory purposes, specifically in five prenatal developmental toxicity studies. Mice were used to assess the modes by which certain substances exert toxic effects. Rabbits were used to assess skin and eye irritation endpoints to meet regulatory requirements in those countries where alternative tests were not accepted. Shell used 11,005 mammals to assess product safety in 2013. While Shell constantly strives to reduce the numbers of animals used, it 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 fewest animals.

TABLE 2: MAMMALIAN SPECIES USED IN 2013

Species	Number
Rats	5,365
Mice	4,766
Rabbits	874
Total	**11,005**

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 going into the future to meet the increasing requirements of the European Union's REACH regulation and other developing global regulatory agendas.





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 2009-2013 is summarised in Table 3. Regulatory requirements in North America were the main reason for the use of fish. In 2013, the total number of fish increased due to an increased operational footprint in North America.

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.

TABLE 3: USE OF FISH, 2009-2013

Purpose of test	2009	2010	2011	2012	2013
HPV Challenge	0	72	0	0	0
Product stewardship	0	0	17	5,060	11,326
Regulatory compliance	50,481	42,913	45,029	34,320	48,966
Total	**50,481**	**42,985**	**45,516**	**39,380**	**60,292**

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.

CONCLUSION

The Shell external Advisory Panel on Animal Welfare has:

- critically reviewed Shell's 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 assure appropriate animal testing;
- discussed their role and their contribution; 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 Advisory Panel on Animal Welfare 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 has been 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 2014

Charles Gentry (independent consultant on laboratory animal science), Panel Chair
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 Establishment Licence Holders Committee UK, Chairman of the Animal Health Trust Animal Welfare and Ethical Review Committee UK, Compliance consultant to the British Antarctic Survey, and a Member of the Home Office Advisory Group on Laboratory Animal Science.

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.

Catherine Willett (Director, Regulatory Toxicology, Risk Assessment and Alternatives, the Humane Society of the United States)

Kate Willett began her career at the Massachusetts Institute of Technology as a developmental biologist studying embryology using the zebrafish as a model system and then joined a start-up company that pioneered the use of zebrafish for preclinical drug testing. Since 2006, she has focused on the science, policy and regulatory aspects of replacing animals as the basis of chemical safety assessment, first as Science Policy Advisor for People for the Ethical Treatment of Animals, and more recently at HSUS and as coordinator of the Human Toxicology Project Consortium (HumanToxicologyProject.org). She has numerous publications on non-animal approaches and advises international companies and governments on the regulatory use of non-animals methods.

Jim Bridges (Emeritus Professor of Toxicology and Environmental Health at the University of Surrey, UK)

Jim Bridges held previous positions in University of Surrey including Dean of Science and founding Head of two large health research and teaching institutes. He has published nearly 400 papers and reviews and trained 98 PhD students. He is a founder of both the British Toxicology Society and EUROTOX. Work for the EU included the Chair of the two Scientific Committees: Emerging and Newly Identified Health Risks, and Toxicity, Ecotoxicity and the Environment as well as several working groups on future risk assessment methodology that have addressed alternatives to animal testing.