EXTERNAL ANIMAL WELFARE PANEL

REPORT FOR 2016

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EXECUTIVE SUMMARY

Shell is committed to ending the need to do testing involving animals and strives to replace animal testing with suitable alternatives, while ensuring that we continue to innovate, develop and maintain safe new products and technologies and that we comply with regulatory requirements.

In 2016, our research and innovation activities focused on developing new strategies in grouping chemicals by using "read-across" in which similar substances use the same data set, specifically for petroleum-derived substances. Solid read-across and grouping approaches enable reductions in animal testing, while helping to ensure product safety. Shell continued the development of innovative screening tests for developmental and reproductive toxicity. Some of these screening tests have successfully been applied internally in our product development process. Confidence in these new tests is increased by sharing our experiences with regulators.

In addition to non-animal screening tests, effort has also been put into the development of computer-based models. This has resulted in a new model predicting the skin and eye irritation potential of substances and mixtures. In combination with non-animal test systems for these toxicity determinations (endpoints), the model contributes to ending the need for animal testing to assess skin and eye irritation. Novel computer models in combination with non-animal test systems have also been used for the assessment of water discharges. The tools provided reliable information on the inherent hazard properties of the effluent (toxicity, hydrocarbon content and bioaccumulation potential) without extensive laboratory testing. By presenting our research at conferences and through publications in peer-reviewed journals, we are contributing to the growing momentum for global regulatory acceptance of these alternative methods. Where required by law, Shell has evaluated product safety using animals and, wherever possible, the outcomes of the animal tests have been used to validate non-animal alternative testing methods.

With regards to the Shell animal use numbers for 2016, regulatory compliance remains the main reason for animal testing, especially in chemical safety testing for the European Union chemical safety regulation REACH, and effluent testing in the USA and Canada. Research and development of alternative methods for effluent testing, as well as sharing best practices in this area, remains a priority.

INTRODUCTION

There are strong ethical, scientific and business reasons to move away from animal testing as the method to demonstrate product safety. However, for the time being, we live in a strictly regulated environment where animal testing is still required to demonstrate the safety of Shell's processes and products.

> **'You were one of the pioneers transparently reporting on animal numbers'**
>
> Animal welfare panel

Shell implements the principles of "3Rs" (replace, reduce, refine) in animal testing wherever possible while meeting legal obligations and protecting human life and the environment. Any Shell-owned or Shell-operated company must follow the company's animal testing standards when performing laboratory-based toxicology experiments on animals, even in countries that have less stringent requirements. Under Shell's standards, animal testing remains the last resort and the use of non-animal tests to generate equivalent information is the first choice.

At least twice every year the External Animal Welfare Panel ("the Panel") examines and comments on the implementation of Shell's animal testing requirements. The Panel works with Shell to ensure good practice in laboratories. It also advises on how Shell should optimise its engagement externally with the development and application of the 3Rs. The membership and terms of reference of the External Animal Welfare Panel are provided at the end of this report.

This report 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 alternatives to traditional animal experimental methods. An overview of animal use by Shell to assess the safety characteristics and environmental impact of its products, operations and manufacturing processes are set out at the end of this report. This report has been reviewed and approved by the Panel.

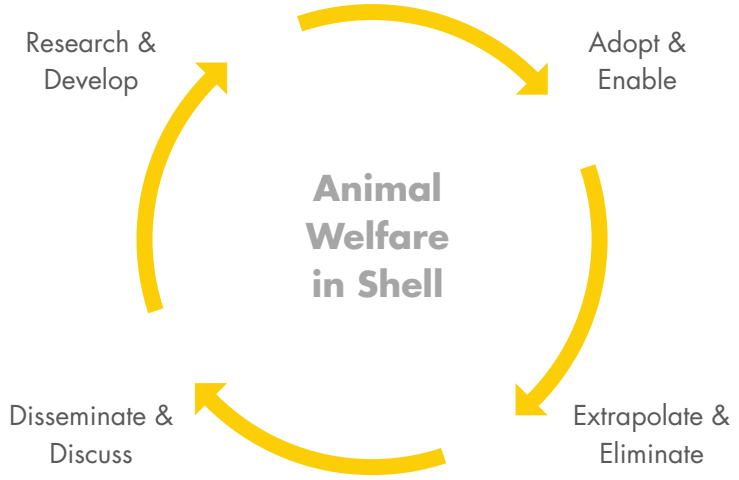
DYNAMIC OF ANIMAL WELFARE ACTIVITIES WITHIN SHELL

Regulatory compliance remains the main driver for animal use in Shell. The approach to animal welfare can be grouped into four activity circles that support the principles of 3Rs. Each activity notes a set of behaviours and mindset that guide Shell subject matter experts on animal welfare with the view of creating and practicing a culture of care. Priorities are selected based on their relevance to Shell's human and environmental safety assessment responsibilities. In addition, focus is given to overcome barriers to the progression of the 3Rs. Priorities are executed in one of the following 3Rs activity circles:

Research and Develop are efforts related to collaboration, funding and conducting research for innovative hazard and exposure assessment methods. Drivers for prioritisation are business need, and areas where the highest impact on the 3Rs can be achieved. Adopt and Enable aims to apply our Research and Develop advances, learnings, and best practices by others into Shell's practices. Shell implements the advancements and insights into internal hazard and exposure assessment activities. In addition, by promoting a culture of care in industry organisations where Shell is active, we can identify and enable best practice for animal welfare and reduce animal testing in product safety and regulatory compliance.

Extrapolate and Eliminate focuses on minimising animal use by leveraging data. Integration of information from multiple sources can be achieved by establishing, utilising and maintaining access to databases. Internally gained insights are extrapolated to external applications to build confidence in the innovative methods. Collaboration with external parties for this is essential. Disseminate and Discuss includes publishing of results, presenting data and ideas in professional fora, engaging with regulators and academic circles. It also includes the teaching of best practice, and review of acquired knowledge by peers, as well as an external panel. This approach aims to instil a culture of care at the highest scientific and practical level. It also intends to generate new ideas that feedback into the activity circles.

The following sections of this report highlight Shell's efforts and progress in each of these activity groups.



RESEARCH AND DEVELOP

Covers Shell's research and other efforts related to collaboration, funding and conducting research for innovative hazard and exposure assessment methods. Drivers for prioritisation are business needs (oil- and gas-derived products), and areas where the highest impact on the 3Rs can be achieved.

Grouping and read-across strategies

Most substances produced by Shell are derived from crude oil or by Fischer-Tropsch (FT) synthesis and are known as substances of unknown or variable composition, complex reaction products and biological materials (UVCBs). These substances are manufactured against physico-chemical specifications (for example, boiling-point range) rather than a specific chemical composition. UVCBs, like single chemical substances, require a thorough assessment of their hazards to enable their safe use.

Global chemical safety regulations prescribe the methods for hazard assessment of substances, and these include methods that test on animals. Considering that there are approximately 600 to 700 individual petroleum substances globally, it is imperative to use so-called "intelligent hazard assessment strategies" which can reduce the use of animals while ensuring adequate hazard assessment. The hazard assessment strategy used by Shell involves 1) grouping of similar substances into "families"; 2) read-across of existing hazard information from one known "data rich" substance to another "data poor" but similar substance; and 3) use innovative non-animal testing methods.

Grouping of substances into "families" for chemical safety assessment is based on the hypothesis that similar substances have similar toxicity or a predictable trend in toxicity. Hazard information can be read-across from one substance to another, provided there is sufficient basis to assume that these substances have similar hazard profiles.

Currently, petroleum-derived and FT-synthetic UVCB's are grouped based on refining history, because their refining or manufacturing history will drive the presence of specific types of molecules with known toxicity profiles.
In 2016, Shell started a joint industry project investigating grouping of petroleum-based UVCBs, focusing on defining biological similarity between substances. This research, performed through the European refining industry environmental science organisation called CONCAWE, is conducted in collaboration with Texas A&M University. The first results demonstrate that petroleum substances can be grouped based on biological profiling (Grimm et al., 2016a, 2016b). Project details can be found here: https://www.concawe.eu/mediaroom/cat-app-project/

Development of non-animal methods for human health protection

iSafeRabbit: New computer model to predict skin and eye irritation
Shell sponsored a challenge from the UK National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs) to develop a computer model to predict skin and eye sensitisation for single substances and mixtures (https://crackit.org.uk/challenge-19-qsars-mix).

The solving of this challenge was awarded to KREATiS and CEHTRA which together developed the iSafeRabbit models for both skin and eye irritation of single substances as well as a software plug-in for calculating values for mixtures. These models can provide qualitative (i.e. classification-based results) as well as quantitative predictions for the skin/eye irritation potential of chemical substances.

The qualitative results indicate whether the substance is non-irritant, irritant or corrosive, while the quantitative result is provided as a Simplified Irritation Index, a new scoring system developed as a part of this project to quantify the irritation potential for skin and eyes. This new system is similar to the traditional rabbit scores (Primary Irritation Index and Draize) but less complex while retaining very similar outcomes to the old methods (Sahigara et al., 2016).

Developmental and reproductive toxicity screening (DART)

Shell continued developing a screening test battery for developmental and reproductive toxicology using a combinatorial approach of a set of three alternative test systems: Dictyostelium discoideum (slime mold), Caenorhabditis elegans (nematode) and embryos of Danio rerio (zebrafish).

Nematode

Over 30 different compounds have been evaluated in the project and it is demonstrated that there is a unique genetic and molecular pattern to potentially predict DART effects, allowing the development of biomarkers and molecular "fingerprint" (Smulders, 2016).

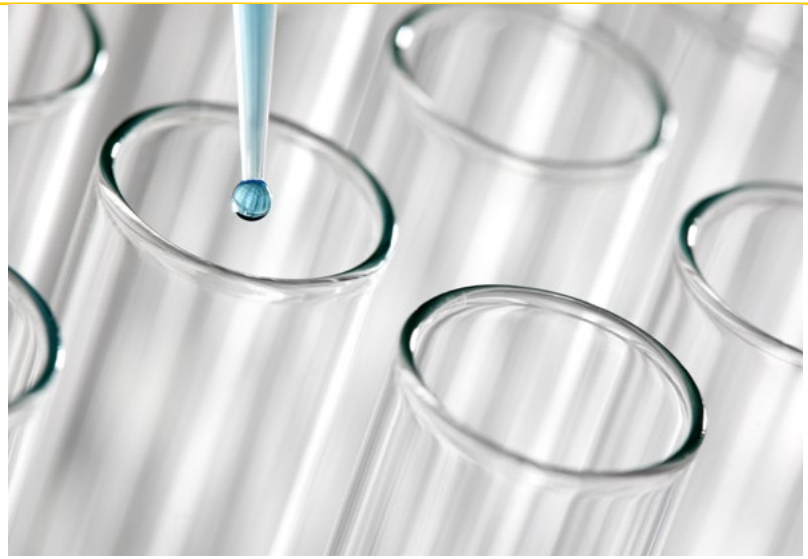
Overall, this project indicates that with the DART screening test battery, developed under the NC3Rs CRACK-IT programme, a high predictive score for developmental and reproductive toxicity can be achieved. (https://crackit.org.uk/challenge-10-predart),
The use of traditional ecotoxicology test species for the prediction of toxicity in mammals highlights the additional value of crossing scientific disciplines (Whale, 2016).

Innovative tools to assess prenatal developmental toxicity have also been used to investigate these endpoints for petroleum substances. The research was conducted in collaboration with the Wageningen University in the Netherlands. It tested the hypothesis that prenatal developmental toxicity observed in some petroleum substances is associated with the presence of 3–7 ring polycyclic aromatic compounds (PACs). The initial phase applying the mouse embryonic stem cell test was successfully completed. The results, supporting the hypothesis that PACs are the primary inducers of the prenatal developmental toxicity in petroleum substances, were presented at the European Teratology Society annual meeting in Dublin, Ireland (Kamelia et al., 2016) and at the 2nd International Conference on Toxicity Testing Alternatives and Translational Toxicology in Hangzhou, China (Boogaard et al., 2016b).

Development of non-animal methods for environmental protection

New screening tools for produced waters

Shell has investigated tools to rapidly assess the persistent, bioaccumulative and toxic (PBT) properties of produced water discharges. Research focused on the development of quick, non-vertebrate screening tools for evaluating hazardous properties and potential risks. This 'toolbox' of simple screening tools, including solid phase micro extraction with gas chromatographic analysis (SPME-GC), in vitro bacterial based toxicity assays (Microtox™) and quantitative structure activity relationship (QSAR) modelling has been developed and applied to the assessment of a number of water discharges that occur offshore (Eadsforth et al 2016b). The tools quickly and cheaply provide reliable information on the inherent hazard properties of the effluent (toxicity, hydrocarbon



content and bioaccumulation potential) without extensive laboratory testing. These tools are typically applied to the first tier of a discharge assessment and the obtained information, together with a dilution assessment, will be used to screen at an early stage and thereby decide whether any subsequent higher-tier assessment with more detailed testing is required (Eadsforth et al 2016b).

Innovative screening tools for environmental hazard and impact assessment

Measurement of environmental parameters like biodiversity, species sensitivity and biodegradability has been improved over the years. One way to estimate impacts on species living in an environment is by catching and assessing live species. Shell has contributed to research where the impact on fish could be assessed using novel, non-lethal methods (Palace et al., 2016). Another method explored to estimate impacts on species in the environment is environmental genomics, which avoids catching live species (Lyon et al., 2016). This is a promising new method that will continue to advance further.

ADOPT AND ENABLE

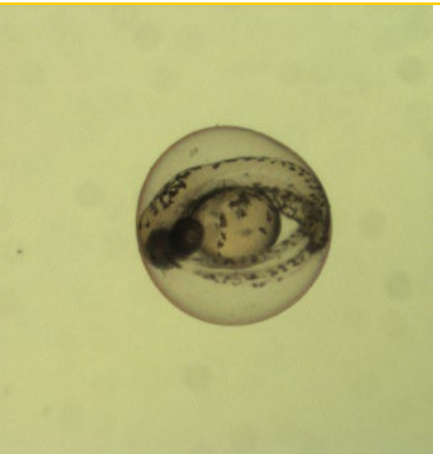
Covers application of our Research & Develop advances, learnings and good practice by others into Shell's practice. Shell implements the advancements and insights into internal hazard and exposure assessment activities. In addition, by promoting a culture of care in industry organisations where Shell is active, we can identify and enable good practice for 3Rs to reduce animal testing in product safety and regulatory compliance.

For the adopt and enable activities, Shell has focused on the application of new and existing non-animal methods, and enabling their use for Shell-specific needs, like petroleum substances. Most currently accepted non-animal assays heavily rely on aqueous solutions, whereas petroleum substances are poorly-water soluble. In addition, existing computational models and read-across strategies tend to focus on single chemicals. However, petroleum and FT substances are UVCBs, so some modifications could be needed for effective application of computational models or read-across strategies

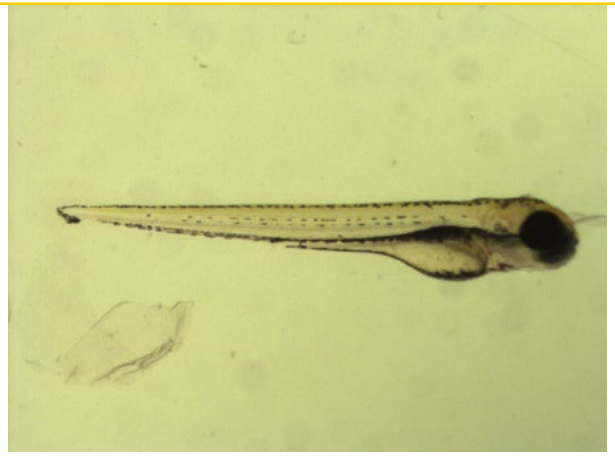
Application of non-animal methods and testing strategies for human health protection

A new test method was applied to a soil and groundwater remediation project at a former refinery site. A specific type of contaminant found in the site's groundwater had no existing local (or global) regulatory reference value that would dictate the level of remediation needed to ensure health and environmental safety (i.e. reduction of contaminant to a low-risk level). In addition to standard literature reviews and computational modelling, Shell decided to address this knowledge gap by developing such a reference value. Shell did this by conducting a site-specific groundwater sample test programme that included acute toxicity testing of a range of aquatic species (fish embryos, water fleas, bacteria and algae) and the human health developmental and

Zebrafish



Zebrafish embryo 2 days post fertilization



Zebrafish embryo 4 days post fertilization

reproductive toxicity assessment using novel screening methods in zebrafish embryos. The toxicity test programme was deliberately designed to avoid use of vertebrate species. The fish embryo toxicity test method (OECD TG 236) was used as an alternative to traditional acute fish toxicity test methods (OECD TG 203 and TSCA 797.1400), potentially saving up to 280 laboratory animals (fish up to the larval stage are not considered animals under EU law). Furthermore, the results of the human health developmental and reproductive toxicity endpoint screening tests in zebrafish embryos were in strong agreement with conclusions from existing mammalian (rodent) reproductive toxicology data for the substances of concern. A traditional developmental toxicity test (OECD 414) would have used around 1,300 rats.

The (eco)toxicology data collated and generated during this project were used to develop ecological and health risk criteria for the substance of concern in groundwater on site. The criteria have subsequently been used to develop remediation/clean up targets for the site which have been shared with and accepted by the local regulatory authorities.

Application of in vitro skin and eye irritation and dermal absorption models for petroleum substances

In a joint industry project by the American Petroleum Institute, the utility of several in vitro skin and eye irritation models for determining the irritation potential of petroleum substances was investigated. A set of four petroleum substances was tested in the standard rabbit skin and eye irritation tests (guideline method OECD 404 and OECD 405, respectively) using the minimal number of three animals per test. The test results were compared with the results from the EpiSkin™ model and EpiOcular™ model (guideline method OECD 439 and OECD 492, respectively). The data demonstrated that the EpiOcular™ test model outcomes correlated well with the animal data on eye irritation of the tested petroleum substances. However, the EpiSkin™ test model outcomes were not fully aligned with the animal skin irritation data of the tested petroleum substances. Further work is needed to improve the applicability of the in vitro tests for assessing petroleum substances.

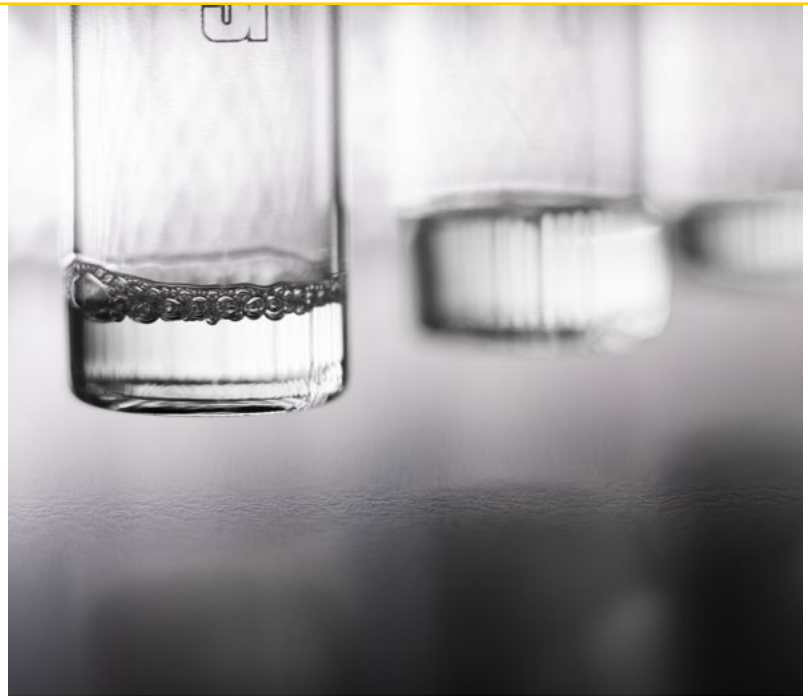
The skin and eye irritation potential of a new fuel formula was assessed using the human three-dimensional epidermal model and the bovine corneal opacity test. These standard methods (guideline method OECD 439 and 437, respectively) confirmed the hypothesised skin and eye irritation potential and have enabled Shell to quickly access the substance's irritation potential following our policy to apply 3R principles in the early development phase of the product. No animals were used.

In an additional study, the dermal absorption of the same new fuel formula investigated using human skin in vitro under different exposure conditions, using a radioactive marker. Skin from various donors was suitable for mimicking fuel-exposure scenarios. From the study, in vitro penetration rates of the fuel additive at the planned formulation rate were established under different exposure conditions, which will be used for risk assessment purposes.

Application of non-animal methods and testing strategies for environmental protection

Petroleum substances are UVCBs and often of limited water solubility. This presents a challenge for environmental protection because exposure is most often in an aqueous environment. Use of SPME, a so-called biomimetic extraction technique, is one method to assess bioavailability and toxicity of substances and effluents without the use of animals. This method compares favourably to calculations using PETROTOX, a QSAR model that has been successfully used to assess aquatic toxicity of petroleum substances (Comber et al., 2016b).

SPME has been used to determine the critical micelle concentration (Haftka et al., 2016) of surfactants, another class of products that Shell manufactures. Because of the surface-active nature of surfactant molecules, they behave quite differently in aqueous environments than many other classes of chemicals and require unique methods to assess their fate and aquatic toxicity. The critical micelle concentration affects a surfactant's bioavailabilty and aquatic toxicity. Other methods have been used for assessing properties of surfactants such as octanol-water partition coefficient (Hodges et al. 2016), biodegradabiltiy, and other parameters that affect fate and toxicity of surfactants (Jackson et al. 2016, Dawick and Lyon 2016).



The PETROTOX model has also been used to understand the effect of biodegradation on crude oil toxicity in aqueous environments without the use of animals. Furthermore, in the event of an oil spill, this will help with predicting effects and help minimise vertebrate testing (Naile et al., 2016). A solid understanding of marine biodegradability is necessary for a good risk assessment as biodegradability and other environmental fate mechanisms are key to determining exposure. Some of the standard methods for measuring biodegradability leave much to be desired and we are working with others to develop improvements to a common marine biodegradation screening test (Ott et al. 2016). In addition, a QSAR model for predicting anaerobic biodegradability of hydrocarbon mixtures has been developed (Lyon et al., 2016a).

EXTRAPOLATE AND ELIMINATE

The extrapolate and eliminate activities focus on minimising the use of tests involving animals by the leveraging of data, for example through replication of learnings and successes across regulatory frameworks. Internally gained insights are extrapolated to external applications to build confidence in the innovative methods. Collaboration with external parties is essential for this.

Collaboration with industry partners: work through consortia to minimise animal use

To meet the requirements of the REACH European chemical safety regulation, Shell typically collaborates with industry partners in a REACH consortium. These consortia comprise the manufacturers and importers of the same substance(s) and forms a platform to share animal data. Working in a consortium enables joint research programmes and avoids duplication of animal testing.

Extrapolate data and eliminate the need for animal testing: weight of evidence and read-across in practice

Shell has published a solid example of read-across for gas-to-liquid (GTL) substances (Boogaard et al., 2016). GTL substances are synthesised by Fischer-Tropsch process from natural gas and have similar functionality and physico-chemical properties to petroleum substances. For the read-across approach, animal data, in vitro test data, physico-chemical properties, and substance composition were used to determine trends for mammalian toxicity. Apparent data gaps were filled with read-across of information from substances within the same group. This approach saved significant animal testing, while maintaining confidence in the hazard information of the substances. For the GTL solvents, Shell has used of a range of screening methods in a weight-of-evidence approach, allowing data extrapolation and elimination of fish testing for acute aquatic toxicity. In order to assess the relative aquatic toxicity of GTL solvents compared with other hydrocarbon solvents, a range of screening methods have been used. These included testing of water-accommodated fractions (WAFs) using SPME, combined with gas chromatography (GC) analysis, Microtox™ and Daphtoxkit F™ assays, and toxicity predictions using the PETROTOX model. Results were compared with compositional information for each of the substances and available experimental data from compliant acute aquatic toxicity studies, conducted under Organisation for Economic Co-operation and Development (OECD) guidelines. Based on the experimental screening methods applied, the two most sensitive approaches for detecting toxicity of the various products are SPME-GC and the Daphtoxkit F™ test kit, whereas the Microtox™ assay is the least sensitive. The PETROTOX calculations predicted a similar relationship with chain length, but were generally more conservative than the experimental data. Overall, using a range of screening methods in a weight-of-evidence approach, the acute aquatic toxicity of GTL hydrocarbon solvents was successfully determined relative to other types of hydrocarbon solvents without the use of vertebrates (Hughes et al; 2016).

DISSEMINATE AND DISCUSS

Shell publishes animal numbers, results from (non)animal testing, and new approaches developed either independently or within a consortium to improve transparency and to share data and best practices. Shell publishes in peer-reviewed journals, presents data and ideas in professional fora, and engages with regulators and academia. The overall goal is to instil a culture of care at the highest scientific and practical levels.

Promotion and discussion of 3Rs in fish testing

Shell chaired a session, for the second consecutive year, on non-vertebrate alternatives for ecological risk assessment at the 43rd Canadian Ecotoxicity Workshop (CEW) held from September 25-28, 2016, in Edmonton, Alberta, Canada. CEW is the foremost ecotoxicology forum in Canada with a scope that includes aquatic and terrestrial environments, and environmental fate. Shell hosted this session to continue to encourage the research community in Canada think about finding alternative methods to traditional vertebrate tests using fish. The aim of this session was to provide a platform to present, discuss and summarise alternative methods and organisational frameworks (i.e. adverse outcome pathways), and to understand the issues that remain in the implementation of these alternative test methods. The session, entitled "Alternative non-vertebrate test methods for evaluating ecotoxicity", specifically invited speakers representing contract laboratories, academia, industry and government. Several of the submissions were related to advances in genomic tools and gene expression as markers for exposure and effects. Shell gave a talk calling for consistency on

fish euthanasia methods (Saunders et al., 2016a, 2016b). Other topics included implementation of the 3Rs in regulatory testing with activities that could greatly reduce vertebrate fish use related to whole effluent toxicity testing for permit testing. Shell was invited by Environment and Climate Change Canada to submit a talk on the use of alternative test methods for whole effluent toxicity testing to their session "New methods and novel approaches for assessing and monitoring environmental contaminant mixtures or individual priority substances" at the 44th CEW meeting in 2017. The outcome will be reported in the 2017 report.

'you show a track record of good practice'

Animal welfare panel

Animal alternatives for whole effluent toxicity testing

In 2016, Shell helped organise and participated in a workshop hosted by ILSI Health and Environmental Sciences Institute Animal Alternatives in Environmental Risk Assessment Technical Committee. This "Concepts, tools, and strategies for effluent testing: an international workshop" aimed to: 1) assess the state of science in effluent toxicity testing globally and foster a better understanding of scientific underpinnings of effluent testing as a tool; 2) survey for current practices of regulators, industry, private laboratories and academia; 3) explore alternative toxicity test methods that may aid in effluent assessments; and 4) assess how to integrate new methods and approaches in regulatory environments. The workshop resulted in the development of two review documents, which will be published in the scientific literature and presented at animal alternatives sessions at the European and North American Society of Environmental Toxicology & Chemistry meeting (Norberg-King et al., 2016a; 2016b). The expectation is that alternative methods will become more accepted and integrated as a part of a "toolbox approach", particularly in areas with developing effluent regulations, and that less reliance on vertebrates for effluent testing will result.

Shell has led a European Chemical Industry Council (known as CEFIC) working group on environmental exposures from exploration activities (Worden et al., 2016) and has actively participated in activities led by European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) on new environmental risk assessment frameworks (Marshall et al., 2016; Maltby et al., 2016; Brown et al., 2016).

Shell use of animals for testing in 2016

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 or Shell joint ventures (JVs) participate are reported separately. Shell reports all experimental animal use on a 100%-basis (each animal is reported in Shell's figures, 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.

Table 1: number of laboratory animals used, 2012 – 2016

Animal used	Tests commissioned	Number of animals per year				
		2012	2013	2014	2015	2016
Fish	Shell	30,832	44,696	61,773	76,476	42,926
Fish	Industry consortia	4,368	5,576	0	2,720	2,285
Fish	Joint ventures	4,180	10,020	20,720	6,260	10,140
Amphibians	Shell	0	0	0	5,770	12,180
Rodents	Shell	150	4,368	2,591	72	0
Rodents	Industry consortia	7,944	5,763	3,202	9,908	767
Rodents	Joint ventures	0	0	0	0	0
Rabbits	Shell	9	870	40	3	0
Rabbits	Industry consortia	6	4	0	20	24
Rabbits	Joint ventures	0	0	0	0	0
	TOTALS	**47,489**	**71,297**	**88,326**	**101,229**	**68,322**

Explanatory 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 JVs where Shell has operational control.

The total number of laboratory animals used from 2012-2016 is shown in Table 1. For 2016, the total number of vertebrates is 68,322.

In 2016, the use of fish for regulatory mandated effluent testing in North-America remained the most significant contributor to the total number of animals used by Shell.

For the second year, amphibians were used as part of a three-year research programme for environmental studies to investigate the impact of oil sands operations on amphibians (see following section).

In 2016, all mammalian testing was carried out through industry consortia. The benefit of performing animal testing through consortia is that following agreed study designs avoids duplication of tests.

Although Shell reports animal numbers on a 100%-basis the specific impact of working through consortia over Shell's total animal numbers is shown in Table 2. If the number of animals used in a consortium study is divided by the total number of consortium partners, a relative 'Shell share' of the total number of animals used is obtained. The calculation shows that from a total of 791 mammals used in consortia, the 'Shell share' was 53 mammals. This clearly demonstrates the impact of working in consortia on the reduction of animal numbers.

TABLE 2: MAMMALIAN SPECIES USED FOR TESTING

Species	Total number	Number used in consortia	'Shell share' of animals used in consortia
Rats	62	62	2
Mice	705	705	50
Rabbits	24	24	1
TOTAL	**791**	**791**	**53**

'incredibly helpful and useful to have insight where the animals are used'

Animal welfare panel

PURPOSE OF TESTING ON ANIMALS 2016

Mammals

The purpose of performing tests on animals is summarised in Table 3. The main driver for testing is regulatory compliance. Although REACH has been the main regulatory driver for obligatory mammalian testing, in 2016 REACH testing requirements were significantly lower than in previous years. This is explained by the fact that testing for the 2010 high-tonnage band chemical registration has been almost completed, with a few tests done in 2016. From the 62 rats used, 50 were used to fulfil standard testing requirements for an ongoing high-tonnage band registration. The other 12 were used to justify a grouping strategy. If this justification is acceptable to regulators, it would potentially allow the consortium to eliminate the need for longer-term animal testing.

Testing on animals for product stewardship purposes covers all testing not directly driven by chemical safety regulations, and mostly helps to understand the mode of action of specific substances, which is essential for 3R principles and validation of in vitro alternatives. Two mechanistic projects that used a total of 705 mice came to maturity in 2016. Additionally, rabbits were used as part of a validation project of in vitro eye and skin irritation test models for representative petroleum substances (more details are reflected in the 'Adopt and Enable' section of this report).

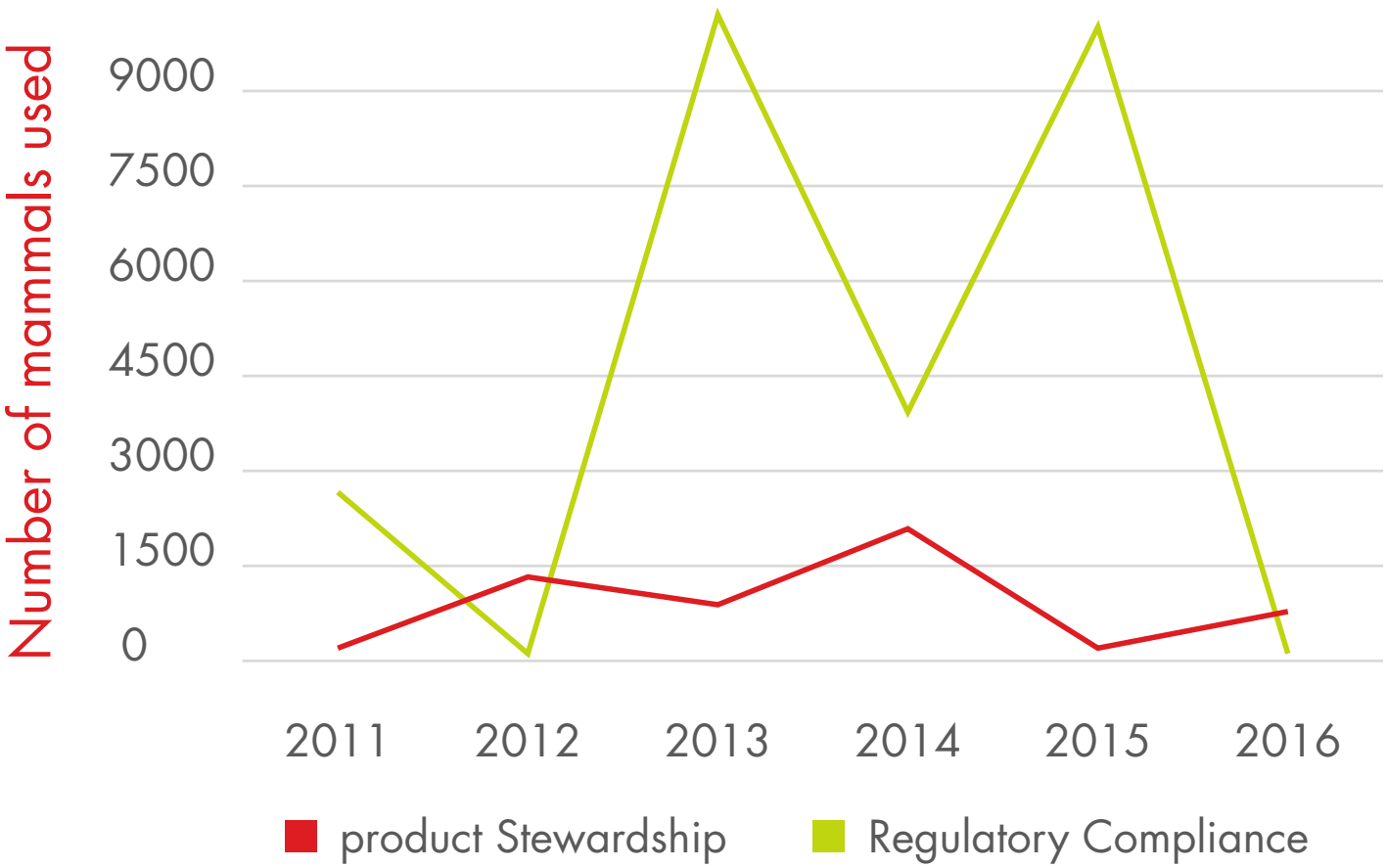
Table 3: mammalian testing by purpose

Test purpose	Number of mammals
Product stewardship*	741
Regulatory compliance	50
TOTAL	**791**

* **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. This mechanism of action can inform the relevance of the used animal model for human risk assessment.

As shown in Figure 1, the number of mammals in tests used for regulatory compliance has significantly increased since 2010 when the EU chemical regulation REACH came into force. The number of animals used in tests for regulatory compliance is closely linked to the REACH registration deadlines and cycles for substance evaluation. Shell registered fewer REACH-related animal testing numbers in 2016. Even though the total numbers of animals used for REACH compliance will vary from year to year, a new peak is expected when the European chemicals agency (ECHA) will require further testing on reproductive and developmental toxicity. Shell will continue to propose and use alternative testing strategies to reduce the number of animals required for product safety where possible within the regulatory framework.

Figure 1: purpose of testing in mammalian species



Explanatory Notes:
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. This mechanism of action can inform the relevance of the currently used animal model for human risk assessment and provide valuable information on likely alternatives
Regulatory compliance: Testing is required by various laws.

FISH AND AMPHIBIANS

Product Stewardship[1] activities in ecotoxicology testing include specific studies on mode of action, which help to reduce the number of standard tests needed under mandatory regulatory requirements. In 2016, 8,480 fish and 12,180 amphibians were used for product stewardship purposes.

In addition to product safety testing, some countries (particularly the USA and Canada) require the use of fish to assess the toxicity of discharges into water. 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. In 2016 this amounted to 83% of all fish tested. This continues to be the largest driver of animal use numbers for across Shell for all vertebrates (mammals, amphibians and fish) at 67%.

Table 4 presents a five-year overview of the numbers of fish required to comply with regulatory requirements and those used for product stewardship purposes.

Off the coast Africa, operations have the regulatory requirement for endemic fish species to be used for effluent testing. This requirement limits the use of alternative approaches.

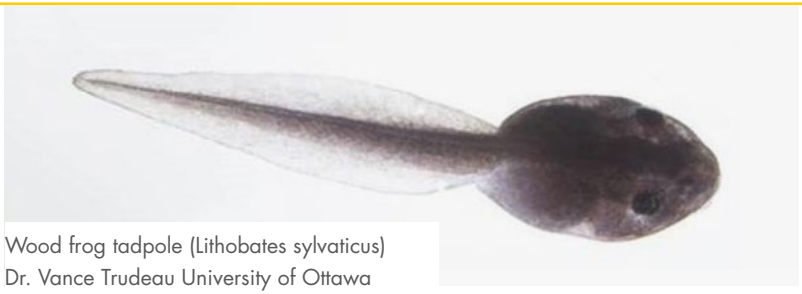
Fish testing for both product stewardship and regulatory testing have experienced considerable decreases from previous years. The main reason has been that a three-year project for the oil sands operations was completed in 2016 (Bailey et al., 2016). The aim of that project was to reduce effluent testing in the longer term and to enable water to be returned to the environment safely. For testing for regulatory compliance purposes there was a substantial increase in testing in 2015 resulting from exploratory drilling in Alaska in 2015, which has since been shut down. Numbers for both product stewardship and regulatory compliance are anticipated to continue to decrease in 2017 because Shell divested several operations in 2016, including its Canadian oil sands operations.

[1] 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. This mechanism of action can inform the relevance of the used animal model for human and environmental risk assessment.

Table 4: use of fish, 2012-2016

Purpose of test	2012	2013	2014	2015	2016
Product stewardship	5,060	11,326	25,960	18,589	8,480
Regulatory compliance	34,320	48,966	56,533	66,867	46,871
TOTAL FISH	**39,380**	**60,292**	**82,493**	**85,456**	**55,351**

Oil sands operations in Canada are required to contain all site process-affected waters in tailings facilities on site. This includes all process waters and groundwater streams that are not used in processing but are in contact with the bitumen ore when mining to permit the recycling of water back into the extraction process and minimise the need for freshwater use. The water return project has been a multi-year study to characterise 10 different water streams on site with full water chemistry and a suite of Environment and Climate Change Canada effluent tests, including some that require fish. Developing water stream profiles allows toxicity prediction. This prediction enables the assessment of the return water to decide whether it is safe for discharge into the environment (Bailey et al., 2016). In this way, a normal hydrological cycle is maintained with the river from which freshwater is taken for ore processing. This project will help us to reduce fish numbers in effluent testing and will lower the overall environmental footprint of the oil sands operations. The water return project was completed in 2016 and, through that effort, six scientific publications have been drafted for publication in 2017. The project found that groundwater from oil sands leases is not toxic and is comparable, if not better, than effluents permitted for discharge in other sectors (i.e. pulp and paper and metal mining industries) in Canada, thus supporting the case for their return to the environment. Additional scientific studies from the water return project have confirmed the identification of constituents responsible for toxicity in oil sands process-affected water, improving the ability to optimise treatment and remediation of process-affected waters (Bailey et al., 2016; Philibert et al., 2016). Finally, Shell performed a study to help optimise the analytical analysis of the organic acid fraction of process-affected water so that greater reliance could be placed on analytical tools for predicting toxicity and further minimise the need for vertebrate toxicity testing.



Wood frog tadpole (Lithobates sylvaticus)
Dr. Vance Trudeau University of Ottawa

Since 2015, amphibians have been used as part of a three-year research programme for environmental studies performed by the University of Ottawa. The aim of this programme is to investigate the impact of oil sands process-affected water on amphibians. Due to their complex lifecycle, there is concern that amphibians might be more sensitive to contaminants than other organisms such as fish and invertebrates. In addition, as wet-landscape approaches are under consideration for post-mine reclamation, frogs will be an integral species in the ecosystem. Furthermore, Environment and Climate Change Canada is developing a standardised frog test method and it is anticipated that frog testing could become a requirement in future risk assessments, permits, or approvals. In the research programme, novel endpoints (e.g. biomarkers like gene expression) will be implemented in addition to traditional toxicity tests for survival and growth to help validate alternative testing methods for understanding exposure and effects on amphibians. So far, the research programme has observed that frogs have comparable sensitivities to fish (Galus et al., 2016; Gutierrez-Villagomez et al., 2016; Orihel et al., 2016; and Philibert et al., 2016), although the final year of the study has yet to be completed. The study will also look at the potential adaptation of local native frogs compared to frogs from an unexposed population to see if frogs in the region have adapted to the natural presence of oil sands in their environment and are now less sensitive than laboratory animals. This study has not been performed with other organisms (i.e. fish and invertebrates) and has been a long-standing question for evaluating the true impacts of oil sands operations.

CONCLUSION

The Shell External Animal Welfare Panel:

- noted that regulatory compliance remains the key driver for conducting animal testing;
- praised progress in alternatives for effluent testing and suggests monitoring progress against the goals;
- recommended exploring whether a chemical's mode of action work could be applied more generally in reducing animal testing;
- recommended that Shell further clarifies how to prioritise its efforts to advance the 3Rs;
- suggested considering the development of new metrics on how Shell is relying on in vitro tests for the basis of decision making;
- suggested illustrating the impact of Shell research projects on animal numbers; and
- suggested continuing advocacy for animal welfare and 3R considerations in regulatory compliance testing.

ABBREVIATIONS

3Rs:	Replacement, reduction and refinement of tests that use animals.
CEFIC:	European Chemical Industry Council
CONCAWE:	The organisation of environmental science for the European refining industry
DART:	Developmental and reproductive toxicity
ECETOC:	European Centre for Ecotoxicology and Toxicology of Chemicals
EU:	European Union
FT:	Fischer-Tropsch synthesis process
GC:	Gas chromatography analytical technique
GTL:	Gas to liquid substances produced by FT.
ILSI:	International Life Sciences Institute
NC3R:	UK National Centre for the replacement, refinement and reduction of animals in research
OECD:	Organisation for Economic Co-operation and Development
PAC:	Polycyclic aromatic compounds
PBT:	Persistent, bioaccumulative and toxic
PETROTOX:	A model that predicts the aquatic toxicity of complex petroleum substances from petroleum substance composition
QSAR:	Quantitative structure activity relationships model
REACH:	The European Union regulation No 1907/2006 concerning the registration evaluation, authorisation and restriction of chemicals.
SPME-GC:	Solid phase micro extraction with gas chromatographic analysis
TSCA:	The Toxic Substances Control Act of the United States of America
UVCB:	Substances of unknown or variable composition, complex reaction products and biological materials
WAF:	Water accommodated fraction methodology.

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NOTE: Poster and presentations are available upon request.

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 Welfare 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 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 2015-16

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. He 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.

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. She 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 the Humane Society of the United States as coordinator of the Human Toxicology Project Consortium (HumanToxicologyProject.org). She published numerous papers on non-animal approaches and advises international companies and governments on the regulatory use of non-animal methods.

Jim Bridges (Emeritus Professor of Toxicology and Environmental Health at the University of Surrey, UK)
Jim Bridges held previous positions in the 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 reviewed and trained 98 PhD students. He is a founder of both the British Toxicology Society and EUROTOX. His work for the EU included as Chair of 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.

Robert Hubrecht (Chief Executive and Scientific Director – Universities Federation for Animal Welfare & the Humane Slaughter Association)
Robert Hubrecht is an ethologist with interests in animal welfare. Prior to joining the Universities Federation for Animal Welfare, he held positions at the Open University and Cambridge University in the UK. His research has included studies of the behaviour, physiology and natural history of farm animals, New World primates (both in captivity and in the wild), and the welfare of kennelled dogs. He has served on numerous advisory committees, including the UK Animal Procedures Committee, the US National Research Council Distress Committee, and expert groups that provided advice on the development of UK and European legislation. He co-edited the 8th edition of The UFAW Handbook on the Care and Management of Laboratory and Other Research Animals. In 2014, he authored the book: The Welfare of Animals Used in Research: Practice and Ethics, Wiley Blackwell.