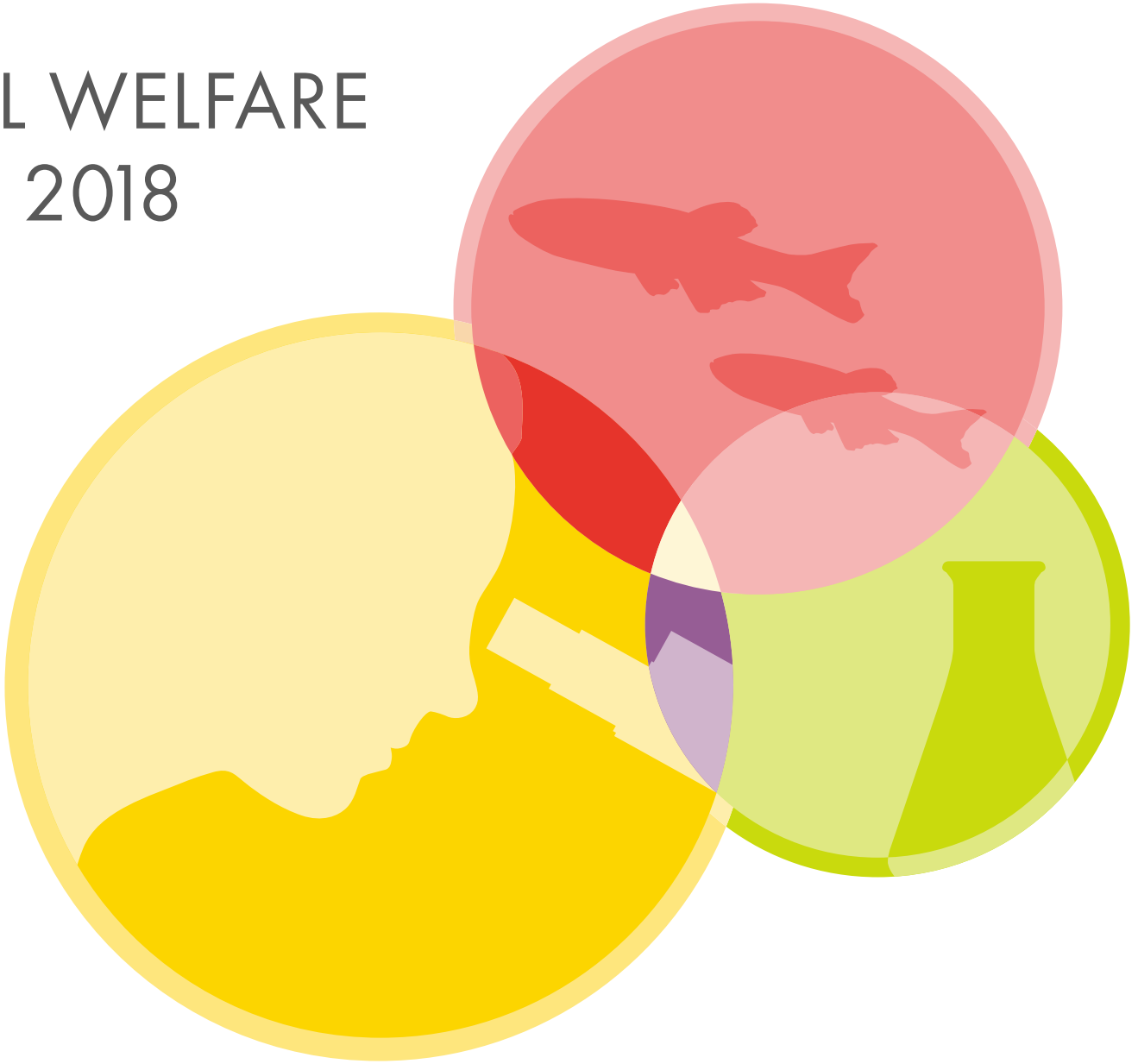
ANIMAL WELFARE REPORT 2018



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EXECUTIVE SUMMARY

It was with great sadness that Shell learned of the death of Charles Gentry on August 26, 2018. Charles chaired the Shell Animal Welfare Panel from 2010-2018, contributing enormously to the development of Shell's policy on animal welfare. His contributions to the Panel and to animal welfare in general are highlighted in this Report. He will be greatly missed.

The data presented in this Animal Welfare Report 2018 (the "Report") are for vertebrate animal use by Shell worldwide. Regulatory compliance remains the main reason for Shell's animal testing, especially in chemical safety testing for the European Union (EU) chemical safety regulation (REACH), and effluent testing in the USA and Canada. Where possible, regulatory compliance tests are carried out with other companies that also seek to comply with the same regulations. This avoids unnecessary duplication of animal tests and minimises the overall use of animals.

Shell continues to work to end the need for animal testing and its strategy is based on the "3Rs": replacement, reduction and refinement. Shell needs to ensure that any alternative safety evaluation enables it to continue to innovate, develop and maintain safe new products and technologies, and to comply with regulatory requirements.

Effluent testing is the largest driver of animals use for regulatory purposes. A priority, therefore, is to explore new approaches to ecotoxicology assessment based on non-vertebrate testing strategies to identify ecotoxic hazards of chemicals and effluents.

Another priority is to optimise the methods for applying products in in vitro tests. Many of Shell's substances are difficult to test (complex multi-constituent substances and/or substances with low water solubility). A study is being carried out to explore different dosing for complex substances to enable increased throughput of non-vertebrate aquatic toxicity tests.

Other work has centred on the further development of an approach to strengthen the substance categories of complex petroleum substances beyond the traditional physico-chemical properties and manufacturing process by adding biological indicators. The approach was refined and applied to the full set of petroleum substances registered under REACH (www.concawe.eu/cat-app). The approach for petroleum substances was presented to the regulatory and academic community in September 2018.

By presenting Shell's research at conferences and through publications in peer-reviewed journals, Shell is contributing to growing the sentiment for global regulatory acceptance of these alternative methods. Where required by law, Shell has evaluated product safety using animals, ensuring where possible that the outcomes of the tests have been used to validate non-animal alternative testing methods.

OBITUARY

Charles Brian Gentry 1949-2018

It was with great sadness that the Shell Animal Welfare Panel learned of the death of Charles Gentry on August 26, 2018, after a short illness.

Charles chaired the Shell Animal Welfare Panel from 2010-2018. He contributed enormously to the development of Shell's policy on animal welfare, particularly by ensuring high standards of animal care were met by external contractors carrying out research or testing on Shell's behalf.

Charles had extensive experience in laboratory animal science, working in senior positions in Australia, the UK and the USA. Charles was dedicated to improving the welfare of animals used in research and played a significant role in encouraging the development and education of animal technicians at institutions where he worked. Charles actively encouraged others to refine their approach to animal care and helped spread best practice across the sector.

From 1998 until 2010 Charles served as Director of the University of Cambridge Biomedical Support Service, a role for which he was, perhaps, most widely known. He was also Certificate Holder and had legal responsibility for compliance with the law relating to all animals use. The certificate holder's job is not always easy, as research on animals can lead to a passionate response from opponents.

Charles had to deal with this pressure, meet the legitimate needs of researchers while ensuring that systems were in place to check work was properly justified and that harm to animals was minimised. Charles walked this tight rope with skill and charm. He was a natural leader, encouraging change and improvement.

Charles was widely respected for his achievements and expertise. After leaving Cambridge he continued to promote education and best practice in laboratory animal science and animal welfare. As Chair of the Establishment Licence Holders' committee, he worked closely with the UK Home Office regulatory unit and also advised institutions in a consultancy capacity and also voluntarily.

Charles was a first-rate chairman, an inspiring speaker and someone who made a real difference to the standards of animal welfare at many organisations. He will be remembered for his achievements, his knowledge and also for his personality. Charles was a true gentleman, good humoured, softly spoken and unfailingly polite and he used these tools to achieve change for the better by consensus. He will be greatly missed.

On behalf of the Shell Animal Welfare Panel, Robert Hubrecht

INTRODUCTION

There are strong ethical, scientific and business reasons to move away from animal testing as the means 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.

The 3Rs (replacement, reduction and refinement) are now broadly accepted as the fundamental ethical framework within which animal research should be conducted. Replacement means the substitution for conscious living higher animals by insentient material; Reduction means reduction in the number of animals used to obtain information of given amount and precision; Refinement means any measure taken to decrease in the severity of procedures applied to those animals which still have to be used (or the provision of better housing and husbandry).

Shell implements the 3Rs principles 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, regulation-required toxicology studies 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.

Replacement Reduction Refinement

At least twice every year, the External Animal Welfare Panel, further details of which can be found starting at page 24 of this Report ("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 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.

3R ACTIVITIES FOR ANIMAL WELFARE

Regulatory compliance remains the main driver for animal use in Shell. The approach to animal welfare can be described by four main activities that support the principles of the 3Rs (replacement, reduction and refinement). 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 of animal tests. The four main activities are:

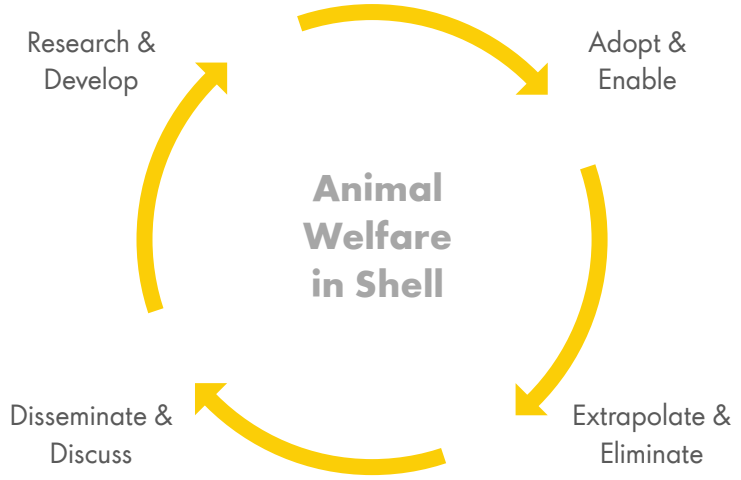
Research and develop are efforts related to collaboration, funding and conducting research for innovative hazard and exposure assessment methods. Drivers for prioritisation are business needs, and areas where the highest impact on the 3Rs can be achieved.

Adopt and enable aims to adopt research advances, learnings and external good practice 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 collaboration to minimise or eliminate animal use by leveraging existing data and prediction models. 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 activity 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 good practice, and review of acquired knowledge by peers, as well as with an external panel. This approach aims to instill a culture of care at the highest scientific and practical level. It also intends to achieve a wide acceptance of insights and to generate new ideas that feed back into the activity circles.

The following sections of this Report highlight Shell's efforts and progress in each of these activities.



RESEARCH AND DEVELOP

The hazard assessment strategy used by Shell involves:

1. the grouping of similar substances into "families" commonly referred as "categories";
2. the "read-across" of existing hazard information from one known "data rich" substance to another "data poor" but similar substance; and
3. the use of innovative non-animal testing methods.

Grouping of substances into categories 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. Read-across avoids duplication of data and significantly reduces the numbers of animals that would be otherwise required.

One of the challenges the petroleum and petrochemical industries continue to face is a reliable risk assessment of their products for human life and the environment that is acceptable to the regulatory authorities as well as society at large. Most petroleum substances and many petrochemical substances are highly complex as they comprise many different molecules. These complex substances are technically referred to as UVCB substances (unknown or variable composition, complex reaction products and biological materials).

Although many regulatory frameworks allow grouping of chemically similar substances into categories and subsequently allow read-across between the members of the categories, this approach is only well-developed for simple, mono-constituent substances.

Our research and development strategy focuses on the development of a grouping methodology for UVCBs as well as on the development of animal-free testing methodologies that are applicable to UVCB substances.

Once the category approach for UVCB substances is accepted, strategic testing of a limited number of category members for specific endpoints and subsequent read across to the entire category would lead to a substantial reduction in animal use.

It should be realised that although the categories are the same for mammalian and environmental toxicological assessments the approaches followed differ since the overall goal of the mammalian toxicological approach is to protect individuals whereas the ecotoxicological methodologies aim to protect entire ecosystems.

Animal-free testing methodologies for UVCB remain a focus for our research, as most novel animal-free testing methodologies rely on water-based test systems which are not suitable for poorly water-soluble UVCBs.

Development of new hazard assessment approaches

Biological read-across for complex substances

Since 2015, Shell has been developing an approach to strengthen petroleum substances categories beyond the traditional physico-chemical properties and manufacturing process by adding biological indicators. To that purpose, in vitro bioactivity parameters were determined in a range of human cell-based models. The data were integrated to derive similarities in bioactivity and chemical composition to characterise the various members of each category and to check the consistency of the categories. The bioactivity data are only to be used for the purpose of categorising these petroleum substances and are not validated for hazard assessment purposes.

After initial proof of concept studies (Grimm et al., 2016) the approach was refined and applied to all petroleum substances registered under REACH (www.concawe.eu/cat-app). In addition to the bioactivity, advanced analytical techniques were used to assess the chemical composition and to quantify the constituents of the tested petroleum substances. The aim was to create not only a biological but also a chemical fingerprint of these substances adding reliability of the categories (Grimm et al., 2017). The approach proved applicable for petroleum substances and was presented to the regulatory and academic community in Brussels in September 2018 (Boogaard, 2018). The final analyses will be conducted in 2019 and the results published.

The same approach of grouping complex substances based on biological and chemical fingerprinting was applied in a case study of two petrochemical olefin families. Clear grouping of the olefin samples based on bioactivity and analytical data was seen for only one family of olefin substances; and much less evident in the second one. Analytical chemistry of neat substances helped understanding the inherent complexity and variability among samples highlighting the importance of complementary analytical information for the development of "biological read-across" (Klaren, 2018).

Elucidating mode of action for targeted hazard assessment

For substances produced at > 1000 tonnes/year, REACH requires the investigation of prenatal developmental effects in two species, an endpoint that requires tests using a significant number of animals (mostly rats and rabbits). As most petroleum substances are produced in volumes >1000 tonnes a year, prenatal development data are also required for the several thousand of individual petroleum substances registered in Europe. Petroleum substances which have complex and varying compositions have been grouped in categories based on composition, refining history, and known commonality in hazards. The purpose is to develop a targeted testing strategy to identify substances with potential prenatal developmental effects, while using a minimum of animal testing. Therefore, a mechanism-based hypothesis approach has been developed, with a focus on specific parts of petroleum products which have distinct effects on the developing fetus.

Polycyclic aromatic hydrocarbons (PAHs) which may be present in heavier petroleum substances may cause prenatal developmental toxicity by interacting with specific genes involved in the development of the fetus. This hypothesis is that PAH contained in some petroleum substances are causing prenatal developmental effects seen in these petroleum substances. This hypothesis was tested in a series of in vitro assays that were exposed to PAH extracts of petroleum substances with different levels of PAH and its results compared to PAH-free synthetic products (gas to liquid – GTL). The results show that the tested PAH extracts of petroleum substances possess hormone modulation activities associated with the quantity and type of PAHs contained in them, whereas none of the PAH-free synthetic products (GTL) were active in the assays. Specific gene activity associated with PAH at cellular level, correlates with in vitro prenatal developmental toxicity effects, suggesting an important modulating effect of PAH toxicity in fetal development. When the results of in vitro activities and chemical composition of petroleum products are combined, it is observed that some classes of petroleum substance may be assigned an "own" signature because of their PAH profile.

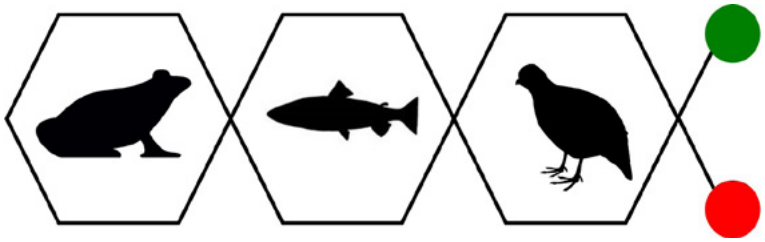
These results are important because they help understanding the role of PAHs in prenatal developmental toxicity tests that REACH requires for petroleum products and confirm that because potency is associated with their collective PAH types and levels, removal of PAH during refinement of petroleum substances is crucial in eliminating this hazard.

Furthermore, knowledge of PAH levels in a petroleum substance combined with targeted in vitro tests may be used to predict the potential to cause prenatal developmental toxicity. This may reduce the need for conventional animal assays, which is a regulatory requirement carried out using two species (Kamelia, 2018).

Novel ecotoxicology methodologies

Eco21 Strategy

In 2018, Shell refreshed its strategy in the exploration of new approach methodologies for the field of ecotoxicology termed "Eco21". The new approach methodologies for ecotoxicology to date have previously focused on the development of models that could be used to estimate toxicity or biodegradability (e.g. Embry et al., 2018a,b; Dawick et al., 2018; Redman et al., 2018). Unlike human health, however, in vitro testing and high-throughput non-vertebrate alternatives for assessing the fate and effects of chemicals in the environment are much further behind in development and regulatory acceptance. The Shell Eco21 strategy involved mapping the various applications of vertebrate use for ecotoxicology assessment within the company (i.e. regulatory requirements and types of products tested (Deglin et al., 2018; Norberg-King et al., 2018; Salvito et al., 2018)), currently available in vitro tools for testing (Campos et al., 2018; Sewell et al., 2018), and endpoints related to effects currently requiring testing. Through this process, research gaps were identified of specific relevance to Shell and research needed for non-vertebrate ecotoxicological assessment was prioritised. As many of Shell's substances have low water solubility and have complex compositions, Shell is working with Texas A&M University to explore different dosing procedures for these substances in in vitro testing systems (i.e. dosing in a multi-well plate) to enable increased high-throughput of non-vertebrate aquatic toxicity tests.



EcoToxChip

The EcoToxChip programme is a multi-institutional and multi-sector collaborative research programme aiming to develop, test, validate and commercialise EcoToxChips (based on quantitative polymerase chain reaction arrays). This will consist of more 300 genes covering key toxicity pathways of regulatory concern in three key vertebrate model species used globally in ecological risk assessment (fish, frog and bird). EcoToxChips will also eventually be developed for three native species of fish, frog and bird of recreational and aboriginal concern in North America.

A data evaluation tool (EcoToxXplorer.ca) has been developed to allow end-users to upload EcoToxChip data and interpret their results for the characterisation, prioritisation and management of environmental chemicals and complex mixtures of regulatory concern.

Shell has been collaborating on the project, providing advice to the research team on end-user needs for the EcoToxChip. To date, most of the 52 exposure studies with standard chemicals and the three model species (bird, frog, fish) required to develop the chips, have been performed, while the organisational framework of genes needed to design the EcoToxChip have been derived.

In 2018, the prototype chips were featured in a booth at the Society of Environmental Toxicology and Chemistry meeting in Sacramento California and gained significant attention from conference attendees. In 2019, Shell plans on trialling the prototype chips with our products as an additional contribution to the development process. The EcoToxChip has the potential to save a significant number of vertebrate organisms. Furthermore, it will help fill a large gap in ecotoxicity data for key vertebrate taxa (i.e., frogs and birds) which is often unavailable or absent for many chemicals.

ADOPT AND ENABLE

The aim is to adopt our research advancements, learnings and external good practice into Shell's practices. Shell implements the advancements and insights into internal hazard and exposure assessment activities. After successful development and use of computer models for several endpoints, including skin irritation, Shell has used the experience to help the development of a model for respiratory sensitisation.

Building models with existing information

The RespiraTox Challenge, funded by the UK's NC3R CrackIT, developed a QSAR model (a computer simulation model), which predicts the potential of individual compounds to cause irritation in the respiratory tract (Wehr, 2018).

QSAR models rely on high-quality datasets. Because there is no specific in vivo toxicity assay for respiratory irritation, empirical information from databases and animal studies was used to develop the model. Results from human volunteer studies for around 100 compounds were included. The final project dataset included more than 2,000 irritating and 800 non-irritating compounds for respiratory irritation which was cross-referenced with physical-chemical and structural properties using machine learning algorithms. Structural properties include the molecular structure, and physical-chemical properties include water-solubility. Although the applicability domain for the models has not been fully characterised, it is worth noting that the use of physical-chemical properties achieves better performance than the use of structural information alone. The current approach will be further refined and improved (e.g. by differentiating sensory and tissue irritation).

The final model will be provided within a user-friendly tool to promote its use by toxicologists, regulators, and any other users to reduce the testing of animals currently used in acute, sub-acute, sub-chronic and chronic studies to assess respiratory irritation. (https://www.item.fraunhofer.de/en/press-and-media/news/respiratox.html).

The work presented here was supported by the NC3Rs CRACK IT Challenge 28: RespiraTox and Shell.

Adaptation of animal models for human relevance

Since 2015, Shell has been reporting on the adaptation of a mouse model to elucidate toxicological mode of action and its relevance to human health. The project finished in 2017 and provided learnings on refinement and relevance of animal tests. The case study is summarised below.

A commodity chemical used in several industrial and household products has been investigated for carcinogenic properties in different test systems. Inhalation of this chemical caused lung cancer in some species and not in others and research was aimed at elucidating whether the mode of action leading to this effect was also relevant for humans. Mode of action investigations started with in vitro studies, followed by studies in animals because in vitro studies were inconclusive. It was consistently demonstrated that mouse-specific genes are responsible for the lung carcinogenic effect. Mode of action studies in animals helped to develop a map of key events explaining why only mice and not humans would develop lung cancer when exposed to this chemical (Andersen, 2018; Cruzan, 2018).

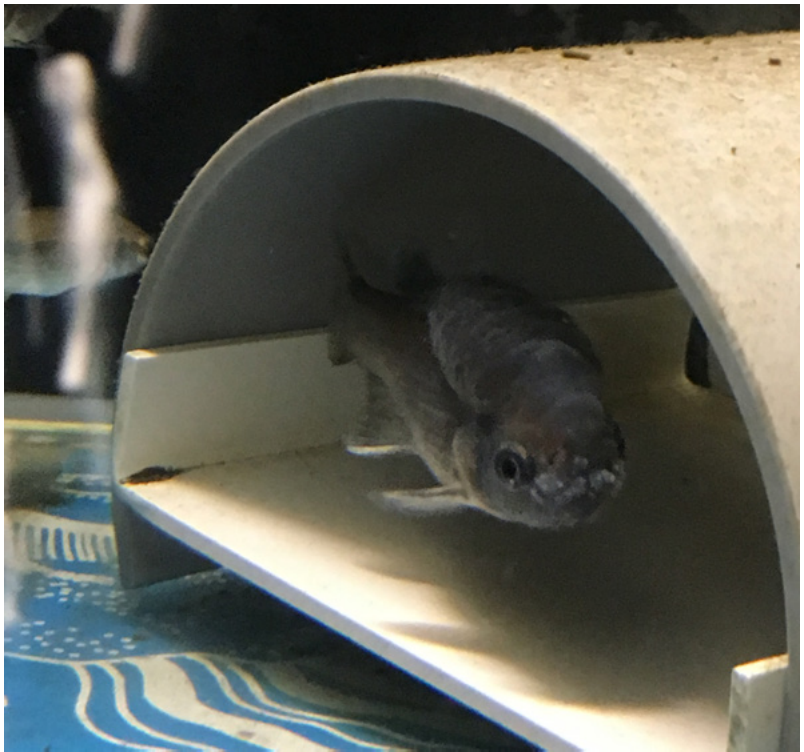
Elucidation of the mouse-specific genetic mechanism that is neither quantitatively nor qualitatively relevant to the human helps in better understanding the relevance of specific animal tests for human risk assessment. This information can be used for the development of tests which have better predictive value for human hazard and risk assessment.

Strategy to reduce fish testing

In 2018, Shell developed a strategy to reduce fish testing and presented it to the Panel. The strategy is to replace and reduce testing on fish by developing and promoting alternative methods. The strategy came from the realisation that the majority of Shell's vertebrate use are fish, of which the majority is stemming from regulatory compliance for testing of effluent or hazardous waste discharges from our facilities in Canada and the USA. Replacing and reducing effluent testing using fish will have the greatest impact at reducing Shell's overall animal usage.

In addition to understanding what is driving Shell's fish numbers each year (e.g. effluent testing), another major component of Shell's fish testing strategy is research of alternative tests available to replace fish testing. Finally, this strategy identifies actions for engaging with the regulatory community to drive the advocacy around acceptance of alternative methods for fish testing. In all, this three-pronged strategy – numbers, research and development, and advocacy – will give Shell the framework and goals to work towards reducing testing with fish. Several aspects of the strategy are already being implemented, with many other activities planned for the years to come.

Work that started in 2018 under Shell's strategy to reduce fish testing included engagement with the key sites that require the majority of effluent using fish testing because of requirements for their effluent discharge permit. Internal reviews were started on the permits mandating these tests, as well as reviews of the historical compliance data using fish. Together these will be used to explore what opportunities there may be to influence effluent testing requirements in the future permit renewals, which occur typically on a five-year cycle. Globally, Shell continued to explore and incorporate new methodologies in effluent testing (Anako et al., 2018; Brown et al., 2018a; Smit 2018a; 2018b; 2018c; 2018d; Whale et al., 2018a; 2018b). Shell also contributed significantly to an article reviewing the future of effluent testing and calling for the next generation of effluent assessment not involving fish (Norberg-King et al., 2018).



EXTRAPOLATE AND ELIMINATE

One of the ways to minimise or eliminate animal use is by using existing data and prediction models. Information from multiple sources is integrated to improve insights.

Read-across for enhanced oil recovery

For the registration of a series of chemicals, which enhance crude oil production, a read-across and testing strategy was developed. The enhanced oil recovery substances are olefinic structures with differing carbon chain lengths. To facilitate a read-across strategy, the longest and shortest carbon chain length products were tested, allowing interpolation of the results to fill data gaps for the other products. This read-across approach was successfully used to submit registrations for two series of enhanced oil recovery substances in North America in 2018 with no additional animal testing needed.

DISSEMINATE AND DISCUSS

To progress on replacement, reduction and refinement of animal use for chemical safety assessment Shell is publishing results of research and development, presenting data and ideas in professional fora and engaging with regulators and academia. This approach aims to instill a culture of care at the highest scientific and practical level among stakeholders. It also intends to achieve a wide acceptance of insights and to generate new ideas that feed back into the Shell activities on 3Rs.

For 2018, external engagement focused on gaining acceptance of the new approach for categorisation of UVCB. This required dissemination of the test results by regular interactions with regulatory authorities and academia as well as the presentation of the concepts and the research outcomes at scientific meetings and in the peer-reviewed literature. The approach concentrates on regions with high regulatory activity such as the EU and the USA and regions where the regulations are still under development and advocacy for the 3R approach might be most effective such as China.

Shell sponsored the 4th International Conference on Toxicity Testing Alternatives & Translational Toxicology and the 2nd Asian Congress on Alternatives, held in Guangzhou, China, in October 2018. At this meeting, international and Chinese representatives from industry, academia and regulatory bodies discussed the development of and experience with novel testing methods for safety testing. Shell presented its experience with methods traditionally used for ecotoxicity testing (a test combination of zebrafish (Danio rerio) larvae, and nematodes (Caenorhabditis elegans)) to assess mammalian developmental toxicity (Smulders et al., 2018).

Shell shared the outcomes of the NC3Rs-funded Respiratox Challenge (Wehr et al, 2018), in vitro approaches used for the grouping of complex olefin streams (Klaren et al., 2018).

21st century methods for ecotoxicity and persistence testing

In 2018, Shell helped organise three workshops related to improving ecological risk assessment. The first was part of the organising committee of the International Council of Chemical Associations' Long-Range Research Initiative (ICCA-LRI) annual workshop with the theme of "Demonstrating 21st Century methods and critical tools for risk-based decisions". The event was organised with Health Canada and U.S. EPA. The workshop brought together international representatives from industry, academia and governmental and non-governmental organisations to address issues of mutual interest in chemical safety and animal alternatives. The workshop agenda included plenary speakers, panel discussions and a poster session highlighting relevant research on the topic of new approach methodologies for chemicals registration. The workshop included case studies of applying 21st century methods in decision-making in human health and ecotoxicology as well as critical tools for risk-based decision making, such toxicogenomics, in vitro to in vivo extrapolation, and persistence and bioaccumulation assessment (Gouin et al., 2018). The key message from the workshop was the agreement that traditional one-for-one validation approach for new methods is outdated and that for new approaches there will need to be a suite of assays and/or information to fit the needs of a regulatory decision.

Approaches that build regulatory confidence and remaining challenges, for example, research gaps, were identified that will need to be addressed to ensure reliability and faster update of alternative methods. The ICCA Long-range Research Initiative (LRI) programmes in Europe, Japan and the USA will use these outcomes to prioritise research in their respective programmes to meet these needs.

Shell also led a joint CEFIC-LRI and CONCAWE workshop on recent developments in persistence and biodegradation assessment in Helsinki, Finland. In addition to organising the workshop and bringing key stakeholders to the table, Shell gave several presentations at the workshop on a range of topics related to improving biodegradation testing (Ott et al, 2018a-e; Whale et al 2018f; Shrestha et al., 2018). The workshop was part of Shell's ongoing efforts to improve understanding of persistence testing in the 21st century (Whale et al., 2018g; Whale et al., 2018h). As persistence is a key component in determining the hazard of a chemical (PBT – persistent, bioaccumulative, toxic) an incorrect assessment can potentially trigger additional animal testing if assessed with inappropriate, non-environmentally relevant test methods. As a result, efforts in the space of improving persistence testing may help reduce future animal testing needs.

Finally, as a continued part of supporting the advancement of alternative methods globally, Shell helped organise a symposium on weight-of-evidence assessment held in conjunction with the Society of Environmental Toxicology and Chemistry (SETAC) Asia-Pacific region meeting in Daegu, Korea. Shell shared industry experiences and applications of weight-of-evidence for regulatory decision-making (Whale et al., 2018d).

Weight-of-evidence assessment is an important component of many new approach methodologies for chemicals risk assessment. Understanding how various new methods all contribute to understanding a chemical's overall fate and toxicity in the environment is a very important concept for understanding environmental risk. Furthermore, weight-of-evidence assessment is recognised to be very important for vertebrate reduction as the framework permits the evaluation or "weighing" of multiple in-vitro assays often needed to needed to replace whole vertebrate tests. At the SETAC Asia Pacific meeting, Shell also shared experiences in using weight-of-evidence methods for assessing the bioaccumulation potential of gas-to-liquids products, which reduced requirements for vertebrate testing considerably (Whale et al., 2018e). This work has also been shared in other forums (Lim et al., 2018) and is now published in scientific literature (Whale et al., 2018).

Shell also continues to lead research in the field of ecotoxicology and ensure work is shared externally at research conferences or in scientific publications where possible (e.g., Ajaero et al., 2018; Brown et al., 2018b; Cserbik et al., 2018; Huang et al 2018a; Huang et al 2018b; Smulders et al., 2018; Van den Brink et al., 2018; Vedagiri et al., 2018; Verheagen et al., 2018).

Disseminate historical information

Efforts are being made to make historical information available to a wider audience. Studies on the relationship between chemical composition and its correlation to carcinogenicity was presented at the Eurotox event in September 2018 in Brussels, Belgium, with the aim to support the continuous use of an industry standard (IP346) which replaced testing in animals (Carrillo 2018a).

A previously unpublished study of a hydrocarbon solvent rich in cycloalkanes was also published in peer review literature indicating that cycloalkanes show similar toxicological effects than isoalkanes, indicating that hydrocarbon solvents with these constituents can be grouped together for read-across purposes and reduce the need for additional animal tests (Carrillo 2018b).

International Society for Exposure Science – European chapter

Exposure science is becoming increasingly more important in the current approach to risk assessment. A better understanding of exposure can significantly improve understanding of risk and enables appropriate risk mananagement. Development of an international network on exposure science is important and Shell contributed to the 2018 meeting of the European chapter of the International Society for Exposure Science (ISES; Dortmund, Germany) by providing the key note lecture on behalf of ECETOC (Meijster, 2018). In this lecture the industry perspective on exposure science was shared. Shell is actively participating in the ISES working groups on exposure modelling and on education in exposure science. The European chapter of ISES has developed a position paper demonstrating the vision on exposure science for Europe. Headlines of this vision include: regulatory alignment (alignment on terminology and requirements, potentially towards a common framework); the identity of exposure science as a discipline on its own right (embedded in university programmes as separate education), and communication as independent scientific discipline.

SHELL USE OF ANIMALS FOR TESTING IN 2018

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 jointly with other companies through, for example, industry consortia).

Testing data is collected from internal sources and from reports provided by external testing laboratories.

The total number of laboratory animals used in procedures from 2014-2018 is shown in Table 1. For 2018, the total number of vertebrates (including mammalian, fish and amphibian species) is 37,689. This total is comparable to the number reported in 2017. In 2018, 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.

Table 1 Number of laboratory animals used worldwide, 2014 – 2018

Animals used	Test commissioned	Number of animals per year				
		2014	2015	2016	2017	2018
Fish	Shell	61,773	76,476	42,926	32,732	34,499
Fish	Industry consortia	0	2,720	2,285	0	1600
Fish	Joint ventures	20,720	6,260	10,140	1,920	720
Amphibians	Shell	0	5,770	12,180	17	0
Rodents	Shell	2,591	72	0	0	105
Rodents	Industry consortia	3,202	9,908	767	1,787	765
Rodents	Joint ventures	0	0	0	0	0
Rabbits	Shell	40	3	0	0	0
Rabbits	Industry consortia	0	20	24	3	0
Rabbits	Joint ventures	0	0	0	0	0
	TOTALS	**88,326**	**101,229**	**68,322**	**36,459**	**37,689**

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. In instances where work was placed for a JV through an industry consortium, the data is reported under industry consortia.

In 2018, the majority of 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 765 mammals used in consortia, the 'Shell share' was approximately 53 mammals. This clearly demonstrates the impact of working in consortia on the reduction of animal numbers.

Table 2 Mammalian species used worldwide for testing

Species	Total number	Number used in consortia	"Shell share" of animals used in consortia
Rats	830	745	51
Mice	40	20	2
Rabbits	0	0	0
TOTAL	**870**	**765**	**53**

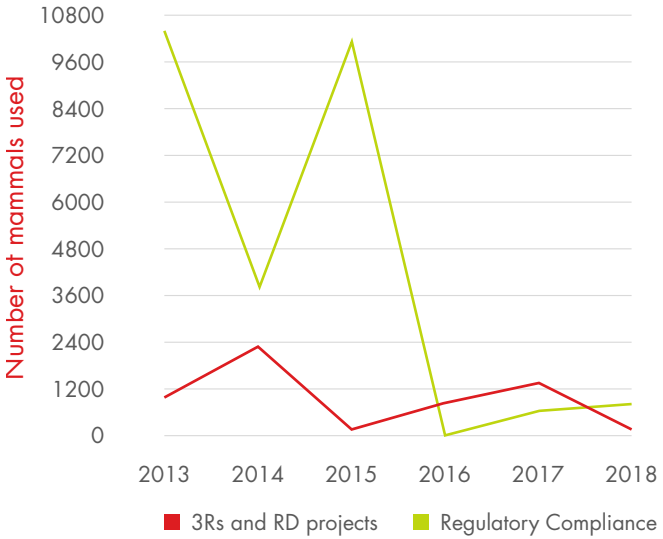
PURPOSE OF TESTING ON ANIMALS IN 2018

Since 2017 Shell has indicated the purpose for animal testing using the categories 3Rs and research" and "regulatory compliance". The purpose of regulatory compliance is self-explanatory, the purpose 3Rs and research is defined as data that is generated to understand the health and environmental hazards of a product and not collected for regulatory purposes, and/or is developed for research aiming to advance the 3Rs. 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, or to develop novel non-animal testing methods.

As Shell is using the 3Rs concepts to promote animal welfare, smart and combinatorial testing strategies are applied. For example, when obliged to conduct an animal test for regulatory compliance, there might be an opportunity to combine the mandated test with a research project which would maximise the use of information obtained from the used animals. This research project would typically generate data to advance 3R methodologies or enhance the information of Shell's chemical portfolio.

As seen in Figure 1, since 2010 the number of mammals used for projects on 3Rs and research have remained stable. However, the number of animals used for regulatory compliance fluctuates from year-to-year. This is because of changing regulatory demands, which can be impacted by global regulations coming into force.

Figure 1 Purpose of testing in mammalian species



In 2018, a total of 870 mammals were used worldwide in tests; 88% of the animals were used in tests carried out in industry consortia (see Table 1) to solely comply with REACH. Animals used by Shell alone for 3Rs and RD projects was 12%. As seen in Figure 2, since 2010, of all tests on mammals for regulatory compliance, 57% has been for REACH purposes alone. The impact of REACH on the total number of mammalian species is significant (44%), when compared to the combined numbers of non-EU regulatory frameworks or 3Rs and research and development figures. REACH compliance has had the highest impact on mammal use since it entered into force in 2010.

Figure 2
(2010-2018)
Tests using mammals for regulatory compliance

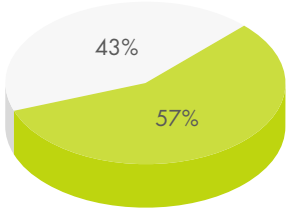
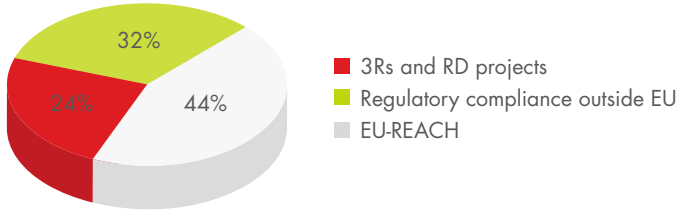


Figure 3
(2010-2018)
Purpose of testing



Shell also conducts testing to advance 3R methods or for research and development purposes to understand the health and environmental hazards of a product that is not mandated for regulatory compliance. This data is also used or generated to advance 3R methods and may include generation of detailed information on the mechanism of toxic action that is informative about the relevance of the used animal model for human risk assessment. This type of data allows grouping chemicals into "categories" to reduce the mandated tests that would otherwise be required for the individual members of the category.

TESTING IN FISH SPECIES

In 2018, no fish were used worldwide for 3R and research activities. This is the first time in more than five years that fish have not been used for research and development activities. All non-mammal vertebrate testing in 2018 stemmed from direct regulatory required fish testing for product registration or whole effluent toxicity testing.

The number of regulatory required fish has increased by around 2,000 fish but still remains lower than 2014-2016. Whole effluent toxicity testing requirements for discharge permits in North America (80%) and hazardous waste disposal in California (15%) continue to be the primary driver for Shell's fish use accounting for a total of 95% of all fish used in 2018.

Table 3 Use of fish, 2014 - 2018

Purpose of Test	2014	2015	2016	2017	2018
3Rs and Research[1]	25,960	18,589	8,480	274	0
Regulatory Compliance	56,533	66,867	46,871	34,378	36,819
TOTAL	**82,493**	**85,456**	**55,351**	**34,652**	**36,819**

[1]3Rs and research: data is required to understand the health and environmental hazards of a product and is not collected for direct 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. This testing is also performed to help Shell understand the potential implications of anticipated future regulatory requirements or applications for new permits (discharges).

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
ECETOC European Centre for Ecotoxicology and Toxicology of Chemicals
GTL Gas-to-liquid substances produced by Fischer Tropsch synthesis
HESI Health and Environmental Sciences Institute
NC3R UK National Centre for the replacement, refinement and reduction of animals in research
PAH Polycyclic aromatic hydrocarbons
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
UVCB Substances of unknown or variable composition, complex reaction products and biological materials

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 2018

Charles Gentry (independent consultant on laboratory animal science), Panel Chair
Charles Gentry was a company director with international expertise in laboratory animal science. He had a specialist interest in compliance with UK and EU legislation, and in the implementation of good practice. He was a former Director and Certificate Holder under A(SP)A 1986 at the University of Cambridge, UK. He was 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, Science Policy, 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 has published a number of 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 around 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 an interest 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

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