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LEGAL DISCLAIMER

The companies in which Shell plc directly and indirectly owns investments are separate legal entities. In this report “Shell”, “Shell Group” and “Group” are sometimes used for convenience where references are made to Shell plc and its subsidiaries in general. Likewise, the words “we”, “us” and “our” are also used to refer to Shell plc and its subsidiaries in general or to those who work for them. These terms are also used where no useful purpose is served by identifying the particular entity or entities. “Subsidiaries”, “Shell subsidiaries” and “Shell companies” as used in this report refers to entities over which Shell plc either directly or indirectly has control. Entities and unincorporated arrangements over which Shell has joint control are generally referred to as “joint ventures” and “joint operations”, respectively. “Joint ventures” and “joint operations” are collectively referred to as “joint arrangements”. Entities over which Shell has significant influence but neither control nor joint control are referred to as “associates”. The term “Shell interest” is used for convenience to indicate the direct and/or indirect ownership interest held by Shell in an entity or unincorporated joint arrangement, after exclusion of all third-party interest.

Forward-Looking Statements

This report contains forward-looking statements (within the meaning of the U.S. Private Securities Litigation Reform Act of 1995) concerning the financial condition, results of operations and businesses of Shell. All statements other than statements of historical fact are, or may be deemed to be, forward-looking statements. Forward-looking statements are statements of future expectations that are based on management’s current expectations and assumptions and involve known and unknown risks and uncertainties that could cause actual results, performance or events to differ materially from those expressed or implied in these statements. Forward-looking statements include, among other things, statements concerning the potential exposure of Shell to market risks and statements expressing management’s expectations, beliefs, estimates, forecasts, projections and assumptions. These forward-looking statements are identified by their use of terms and phrases such as “aim”, “ambition”, “anticipate”, “believ”, “could”, “could”, “could”, “estimate”, “expect”, “goals”, “intend”, “may”, “milestones”, “objectives”, “outlook”, “plan”, “probably”, “project”, “risks”, “schedule”, “seek”, “should”, “target”, “will” and similar terms and phrases. There are a number of factors that could affect the future operations of Shell and could cause those results to differ materially from those expressed in the forward-looking statements included in this report, including (without limitation): (a) price fluctuations in crude oil and natural gas; (b) changes in demand for Shell’s products; (c) currency fluctuations; (d) drilling and production results; (e) reserve estimates; (f) loss of market share and industry competition; (g) environmental and physical risks; (h) risks associated with the identification of suitable potential acquisition properties and targets, and successful negotiation and completion of such transactions; (i) the risk of doing business in developing countries and countries subject to international sanctions; (j) legislative, judicial, fiscal and regulatory developments including regulatory measures affecting climate change; (k) economic and financial market conditions in various countries and regions; (l) political risks, including the risks of expropriation and renegotiation of the terms of contracts with governmental entities, delays or advancements in the approval of projects and delays in the reimbursement for shared costs; (m) risks associated with the impact of pandemics, such as the COVID-19 (coronavirus) outbreak; and (n) changes in trading conditions. No assurance is provided that future dividend payments will match or exceed previous dividend payments. All forward-looking statements contained in this report are expressly qualified in their entirety by the cautionary statements contained or referred to in this section. Readers should not place undue reliance on forward-looking statements. Additional risk factors that may affect future results are contained in Shell plc’s Form 20-F for the year ended December 31, 2021 (available at www.shell.com/investor and www.sec.gov). These risk factors also expressly qualify all forward-looking statements contained in this report and should be considered by the reader. Each forward-looking statement speaks only as of the date of this report. Neither Shell plc nor any of its subsidiaries undertake any obligation to publicly update or revise any forward-looking statement as a result of new information, future events or other information. In light of these risks, results could differ materially from those stated, implied or inferred from the forward-looking statements contained in this report.

Shell’s net carbon footprint

Also, in this report we may refer to Shell’s “Net Carbon Footprint” or “Net Carbon Intensity”, which include Shell’s carbon emissions from the production of our energy products, our suppliers’ carbon emissions in supplying energy for that production and our customers’ carbon emissions associated with their use of the energy products we sell. Shell only controls its own emissions. The use of the term Shell’s “Net Carbon Footprint” or “Net Carbon Intensity” are for convenience only and not intended to suggest these emissions are those of Shell plc or its subsidiaries.

Shell’s net-Zero Emissions Target

Shell’s operating plan, outlook and budgets are forecasted for a ten-year period and are updated every year. They reflect the current economic environment and what we can reasonably expect to see over the next ten years. Accordingly, they reflect our Scope 1, Scope 2 and Net Carbon Footprint (NCF) targets over the next ten years. However, Shell’s operating plans cannot reflect our 2050 net-zero emissions target and 2035 NCF target, as these targets are currently outside our planning period. In the future, as society moves towards net-zero emissions, we expect Shell’s operating plans to reflect this movement. However, if society is not net zero in 2050, as of today, there would be significant risk that Shell may not meet this target.

Forward Looking Non-GAAP measures

This report may contain certain forward-looking non-GAAP measures such as [cash capital expenditure] and [divestments]. We are unable to provide a reconciliation of these forward-looking Non-GAAP measures to the most comparable GAAP financial measures because certain information needed to reconcile those Non-GAAP measures to the most comparable GAAP financial measures is dependent on future events some of which are outside the control of Shell, such as oil and gas prices, interest rates and exchange rates. Moreover, estimating such GAAP measures with the required precision necessary to provide a meaningful reconciliation is extremely difficult and could not be accomplished without unreasonable effort. Non-GAAP measures in respect of future periods which cannot be reconciled to the most comparable GAAP financial measure are calculated in a manner which is consistent with the accounting policies applied in Shell plc’s consolidated financial statements.

The contents of websites referred to in this report do not form part of this report.

We may have used certain terms, such as resources, in this report that the United States Securities and Exchange Commission (SEC) strictly prohibits us from including in our filings with the SEC. Investors are urged to consider closely the disclosure in our Form 20-F, File No 1-32575, available on the SEC website www.sec.gov.
ABBREVIATIONS

3Rs: Replacement, reduction and refinement of tests that use animals.
AOP: Adverse Outcome Pathways are models that identify the molecular events required to produce a biological effect
EST: Embryonic Stem Cell Test
NAM: New approach methodologies refer to any alternative test methods and testing strategies that do not require vertebrate animals
OECD: Organisation for Economic Co-operation and Development
PAH: Polycyclic aromatic hydrocarbons
QSAR: Quantitative structure-activity relationship is a computational modelling method for identifying relationships between structural properties and biological activities of chemical compounds
REACH: 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
ZET/ZETA: Zebrafish Embryotoxicity Test/Zebrafish Embryo Teratogenicity Assay
EXECUTIVE SUMMARY

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

The data presented in this Animal Welfare Report 2021 (the “Report”) are for vertebrate animal use by Shell worldwide. The main reason for Shell’s use of animals for testing remains regulatory compliance, especially with respect to effluent testing in the USA and Canada, and chemical safety testing for the European Union (EU) chemical safety regulation (REACH). Where possible, regulatory compliance tests are conducted 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 will continue to prioritise research on alternative test methods to assess ecotoxic hazards of chemicals and effluents in fish.

In 2021, Shell continued to develop and implement procedures to ensure animal care and welfare for its growing portfolio of low-carbon renewable fuel projects that use waste biomass from animals kept for food production. Shell is committed to ensuring animal welfare principles are implemented and adhered to in the use of these new fuel sources. Shell will continue to seek guidance on how best to engage and ensure the welfare of animals involved in production of animal-based biomass through our animal welfare panel.

Another priority is to develop new and advance acceptance of in vitro test methods used in assessing reproductive and developmental toxicity, which require large numbers of animals. This strategy has been applied to the risk assessment of Polycyclic Aromatic Hydrocarbons in complex petroleum-derived substances, which can be difficult to test using traditional methods. Both in vitro and in silico methods have been utilised to accurately predict developmental toxicity. This research will also support the use of existing data when applied to other substances that lack testing data.

Other work has centered on using existing information to establish standardised protocols for tests that do not involve animals. Collaborative research in this area has highlighted gaps in method standardisation, reporting requirements and endpoint assessment, all of which can hamper regulatory acceptance of novel, non-animal test methods. This work will increase acceptance of these alternative assays and replace the need for additional animal testing.

Shell has collaborated with several academic and industry partners to develop tools and alternative methods for chemical risk assessment. Shell actively works to publish research in peer-reviewed journals and present at conferences and scientific forums, which contribute to the discourse on regulatory acceptance of alternative test methods for risk assessment. Due to the COVID-19 pandemic, in-person involvement and presentations at public forums has decreased in some areas. As virtual/hybrid conferences gain popularity and conferences resume in-person attendance, Shell will continue to engage in opportunities to present research in a public forum.

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INTRODUCTION

There are strong ethical, scientific, and business reasons to move away from animal testing as the primary method for demonstrating the safety of products and processes. For the time being, however, we live in a strictly regulated environment where animal testing is still required to show this.

The 3Rs (replacement, reduction, and refinement) are the fundamental ethical framework within which animal research should be conducted. Replacement, means replacing animal tests with non-sentient methods such as fish embryos, cell lines, or computer models instead of conscious vertebrate animals. Reduction, means lowering the number of animals used within a test or study to obtain the same degree of information. This can be achieved by appropriate experimental design, accurate statistical evaluation, read across, and cost-sharing via consortium involvement. Finally, refinement, refers to any measure that decreases the severity of procedures applied to those animals that are used in tests such as the provision of better housing, husbandry and the selection of humane endpoints.

Shell applies the 3Rs principles in its product safety assessments wherever possible, while meeting legal obligations and protecting human health and the environment. Any Shell-owned or Shell-operated company must follow the company’s animal testing standards when performing laboratory-based eco/toxicology studies on vertebrates, even in countries with less stringent requirements. Under Shell’s standards, animal testing remains the last resort. Our first choice is always to avoid using animals.

Each test that does require the use of animals, goes through the internal justification and approval process. This process includes a review of the test purpose (regulatory or research and development), number and type of animals to be used, the selected standardised test method and ensures there is no non-animal alternative available. This first step also includes a review of any 3R principles that have been applied. For example, that the number of animals used has been reduced or replaced compared to the standard tests, and that animal care and husbandry has been improved. Once an animal test has been approved, the study is initiated.
We produce our reports the year that follows the study, meaning animal testing completed in 2021 is compiled and reported in 2022. Upon completion of the animal test, Shell (or as part of a consortium) receives a draft study report from the lab, which includes the overview, procedures and outcomes of the animal test. This draft report is reviewed by Shell and any other companies involved prior to finalisation of the report and provides the total animal numbers used for the study. The animal welfare team at Shell then compiles the data from all animal tests for inclusion into the Shell Animal Welfare Report.

At least twice a year, the external and independent 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 throughout Shell’s animal welfare activities. 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 advancing new and alternative testing methods (e.g., in vitro tests). It describes Shell’s external engagement and advocacy for alternatives to traditional animal experimental methods. The Report also contains an overview of Shell’s use of animal testing to assess the safety characteristics and environmental impact of its products, operations and manufacturing processes.

The 2021 Shell Animal Welfare Report marks 20 years of Shell assessing and reporting on the company’s use of animals and progress in the 3Rs. As the science around animal alternatives has evolved and in the face of a dynamic regulatory landscape over the last 20 years, Shell has been innovative and committed to the development and refinement of non-animal test methods. A 20-year review of Shell’s progress in animal welfare will be published as a separate report.

This Report has been reviewed by the Panel who have provided advice related to animal welfare and constructive feedback that will help us progress our aims regarding the 3Rs.
3RS ACTIVITIES FOR ANIMAL WELFARE

Animal testing in 2021
The main reason for Shell’s use of animals for testing remains regulatory compliance that determines the hazard and risks chemicals pose to humans and the environment.

Animal testing is required to assess the level of chemical hazard, regardless of how much exposure risk there is for a substance. Animal testing guidelines are frequently updated and extended to cover potential new hazards, which increases the number of animals needed for tests. The updates also mean that chemicals may need to be re-tested because previous studies might be deemed “inadequate” on the grounds that they were performed under “outdated” protocols. While Shell sees chemical safety evaluation as paramount, we strongly believe that ever-increasing animal testing does not necessarily improve overall safety assessments. Existing scientific knowledge and alternative methods can be combined to assess potential new hazards and minimise animal use while ensuring safe use of chemicals.

Regulatory frameworks (eg., REACH in the EU) rely heavily on animal tests following primarily the Organisation for Economic Co-operation and Development (OECD) test guidelines. A strict interpretation of the requirements may result in focusing solely on the animal test itself to fulfil a regulatory formality, rather than the outcome or protection goal of the assessment. A focus on the outcome of a chemical safety assessment instead will create opportunities to explore novel and alternative ways of assessing chemical safety while benefiting animal welfare.

The Shell strategy on animal testing can be described using four main activities that support the principles of the 3Rs (replacement, reduction and refinement). Each activity describes the mindset and behaviours that guide Shell’s subject matter experts (SMEs) on animal welfare as they seek to create and practise a culture of improvement and care. They select their priorities according to Shell’s responsibilities to assess human and environmental safety. They also focus on any obstacles to applying the 3Rs for animal tests. The four main areas of the strategy are:

Research and develop, which refers to efforts focused on collaborating, funding and conducting research on innovative ways of assessing hazard and exposure. These are prioritised according to business needs and areas where the highest impact on the 3Rs can be achieved.
**Adopt and enable**, which refers to absorbing external good practice, research advances and new knowledge into Shell’s ways of working. Shell implements the advances and insights into its assessments of hazard and exposure. By promoting a culture of care in industry organisations where Shell is active, we also aim to identify and adopt best practice for animal welfare and to reduce animal testing in product safety and regulatory compliance.

**Extrapolate and eliminate**, which minimises animal testing through collaboration and the use of existing data and prediction models. By establishing, using and maintaining access to databases, it becomes possible to integrate information from multiple sources. Internally gained insights are extrapolated to external applications to build confidence in innovative methods. For this activity to succeed, collaboration with external parties is essential.

**Disseminate and discuss** includes publishing results, presenting data and ideas in professional forums and engaging with regulators and key academics. It also includes the sharing of good practice and the review of acquired knowledge by peers and an external Panel. This approach aims to instil a culture of care at the highest scientific and practical level and potentially reduce animal testing. It also seeks to achieve a wide acceptance of insights and generate new ideas that can be put into practice.

The following sections of this report highlight Shell’s efforts and progress in each of these activities.
RESEARCH AND DEVELOP

Developmental toxicity is a key endpoint assessed under regulatory requirements by in vivo methods. Shell aims to collaborate on research that allows it to innovate with ways of assessing hazard without using tests on animals and thereby encourage the acceptance of methods such as in vitro tests.

Advances in non-animal test methods for developmental toxicity testing

Developmental toxicity testing is an animal-intensive endpoint and has historically required large numbers of animals. Several complex petroleum-derived substances (petroleum UVCBs) may contain polycyclic aromatic hydrocarbons (PAH). The industry is expected to generate insight into the developmental toxicity of PAH found in UVCB substances. To help overcome this challenge, and in partnership with a university, this project used currently available embryonic stem cell test (EST) data in combination with physiologically based kinetic (PBK) modelling data to predict the developmental toxicity of PAH, using benzo[a]pyrene (BaP) as a model compound. Using this approach, an in vitro concentration-response curve was translated into an in vivo dose-response curve to assess developmental toxicity of BaP after single or repeated dose exposure. The developed model accurately predicted the in vivo developmental toxicity of BaP based on the in vitro data from the EST. This model represents a promising strategy of using in vitro-in silico data to accurately predict developmental toxicity of PAH (Wang et al. 2021).

3Rs Benefit

Well-validated in vitro test methods such as zebrafish embryotoxicity test (ZET) and EST can be used to assess the developmental toxicity of petroleum derived UVCBs. For example, results using fume condensate extracts of bitumen and oxidized asphalt do not cause in vitro developmental toxicity, in agreement with the in vivo test results. This approach may also be of use to support read-across from other petroleum substances that have in vivo data and help fill the data gap to similar petroleum substances lacking developmental data. This study emphasises the utility of in vitro alternative assays in predicting developmental toxicity (Kamelia et al. 2021).

3Rs Benefit

This approach can then be applied to other petroleum substances and further validate the use of ZET and EST in assessing developmental toxicity. These efforts will prevent duplication of data for similar substances and help reduce and replace animal use.
ADOPT AND ENABLE

We aim to adopt our research advances and external good practice into Shell’s ways of working. Shell incorporates the advances and insights into its methods of assessing hazard and exposure.

Using existing information to standardise protocols for new methodologies

For several years Shell has actively worked on alternatives to mammalian animal testing for reproductive and developmental toxicity assessment of chemical substances. Currently Shell is involved in two leading initiatives in this area viz DARTpaths (https://nc3rs.org.uk/crackit/dartpaths) and EFRO 3R TOXFLOW (https://www.kansenvoorwest2.nl/en/projecten/3r-toxflow/).

In these projects the focus is on the development and acceptance of assays in worms (C. Elegans) and zebrafish embryos as alternatives to mammalian animal tests. Shell has participated in collaborative work to further the acceptance of these assays by helping to establish standardised protocols and reporting criteria for carrying out reproductive and developmental toxicity testing in non-animal methods (van der Voet et al. 2021).

3Rs Benefit

Research indicates that these models can be used to assess the reproductive and developmental toxicity of chemicals without the use of animal-intensive methods, thereby replacing traditional methods with non-animal methods for assessing toxicity.

New approach methodologies (NAM) for mammalian reproductive hazard assessment can potentially lead to large reductions in mammalian tests under REACH. The zebrafish embryo teratogenicity assay (ZETA) as a whole-organism model has gained recognition among NAM to predict human developmental toxicity because it incorporates the complex embryonic developmental processes and overcomes limitations of in vitro methods. A comprehensive literature review identified a lack of standardisation of the ZETA regarding experimental procedures and endpoint assessment. ZETA method standardisation needs to be addressed for better regulatory acceptance of the method. As an attempt to improve this situation, a set of minimum reporting requirements regarding the ZETA protocol were proposed to support method standardisation and validation criteria. These efforts are expected to advance the regulatory acceptance of the ZETA for teratogenicity screening in chemical toxicity assessment (Di Paolo et al. 2021).

3Rs Benefit

The findings from this review will support ongoing validation efforts towards regulatory acceptance of ZETA and help replace animal test methods with alternatives such as ZETA.

Animal Welfare and The Energy Transition

In 2020, Shell announced its target to become a net-zero emissions business by 2050 and in 2021 Shell reported an 18% reduction in emissions over 2016 amounts (https://reports.shell.com/energy-transition-progress-report/2021/introduction/chief-executive-officers-introduction.html). As a part of our actions towards our net-zero target, waste biomass and biocomponents from animals bred or kept to produce food or feed will be used as low-carbon fuel feedstocks. For example, rendered animal fats (tallow), which are not suitable for use in the food chain, will be used to produce renewable diesel and sustainable aviation fuel (SAF). Manure from animals such as dairy cattle will be digested and used to produce renewable natural gas (RNG), otherwise known as biomethane, which can be liquified or compressed to power heavy duty vehicles or used as a substitute for liquified natural gas to power homes and industry.

These new uses of animal biocomponents create a need for increased support and leadership related to animal care and welfare within
Shell is committed to working with the Panel to ensure the animal welfare principles are implemented and adhered to.

**Dairy Renewable Natural Gas**
Currently Shell has four RNG facilities in development in the U.S. They are part of a broader portfolio of Shell anaerobic digestion projects supporting the use of Renewable Compressed Natural Gas (R-CNG), a low-carbon alternative for road transport.

We work with our suppliers on a case-by-case basis, however in the US, we are partnering with the National Dairy Farmers Assuring Responsible Management (FARM) Animal Care Program, developed by the National Milk Producers Federation (NMPF) as well as the Innovation Center for US Dairy. FARM Animal Care is one of the first livestock animal care programmes in the world to gain compliance with the ISO standard TS 34700. The standard ISO TS 34700 is a science-based international standard on Animal Welfare Assessment based on the OIE (World Organization of Animal Health) standards. FARM Animal Care performs animal care evaluations on dairy farms by certified evaluators on aspects such as: the herd’s overall condition, herd cleanliness and health, strong veterinarian relationships, farmer and employee training and animal handling, implementation of best management practices for all animals including calves, sick animals and mature cows, development and implementation of protocols, and recordkeeping which demonstrate compliance to the standards. The FARM program performs third-party verifications on a subset of dairies annually as well as having task forces review the latest animal-welfare science on key animal care issues in the dairy industry to ensure the programme incorporates the latest in science-based animal care and welfare practices.

We also participate in the Dairy Cattle Welfare Council (DCWC) ([https://www.dcwecouncil.org/](https://www.dcwecouncil.org/)), an organisation with the purpose of advancing dairy cattle welfare by bringing together dairy farmers, veterinarians, consultants, universities and the dairy community to develop best recommended practices with focus on animal wellbeing, management, husbandry, animal-person interaction, health and productivity. The DCWC supports continuous improvement of animal wellbeing on dairy farms.
HEFA Biofuel
Shell’s hydropricessed esters and fatty acids (HEFA) and co-processing technology converts crop oils, such as rapeseed oil, animal fats (tallow) and waste feedstocks (e.g., used cooking oil), into a range of low-carbon fuels (LCF), including renewable diesel and SAF. Shell is transforming many of its manufacturing operations to produce HEFA biofuels. To ensure that the tallow purchased does not violate animal care and welfare principles, Shell aims to purchase biocomponents that have been certified against recognised and credible multi-stakeholder voluntary sustainability standards such as the Roundtable on Sustainable Biomaterials (RSB) and the International Sustainability and Carbon Certification (ISCC). Because this is not always possible, Shell carries out its own due diligence and works with renderers and suppliers to improve animal care and welfare standards in our supply chain.

The Panel is in place to provide feedback and guidance to improve Shell’s animal welfare initiatives. We will continue our efforts to contribute positively to improving agriculture animal welfare as we have with animal testing.

3Rs Benefit
This work will deliver higher welfare standards and represents progress in our goal of refining Shell’s animal welfare practices.
EXTRAPOLATE AND ELIMINATE

One way to minimise or eliminate animal testing is by using existing data and prediction models. Information from multiple sources can be integrated to improve insights, in areas such as risk assessment.

**Use of existing databases for better hazard assessment**

As part of an endocrine disruptor assessment for a chemical (dicyclopentadiene-DCPD) being used in the resins industry, together with industrial partners, Shell assessed the potential endocrine activity of DCPD based on currently available data. Using information from animal data in addition to animal alternative information such as the quantitative structure-activity relationship model (QSAR) and in vitro data, the working group derived a conclusion indicating that the substance does not function via an endocrine mode of action (Tencalla et al. 2021).

**3Rs Benefit**

Without generating new animal data, the combination of available animal test data with in vitro and QSAR data allows for maximisation of existing results, providing a better understanding of hazard data and predictions. This approach reduces the need for additional animal testing and can also highlight if or where additional testing may be necessary.

Skin and eye irritation are key human health endpoints assessed by in vitro and in vivo methods, and provide data which allow for chemical classifications under the UN GHS criteria. Traditional scoring systems to quantify in vivo irritation potential of chemicals (Primary Irritation Index for Skin and Modified Maximum Average Score for Eyes) require a quantitation of several subjective in vivo observations leading to difficulties in translating an irritation score to a chemical classification system. This study was able to determine a chemical classification can be driven by one observation (for skin) and two observations (for eyes), allowing for a more simplified system for assessing irritation and corrosion. The system (The Simplified Irritation Index) is based on validated studies across several chemical groups, demonstrating its robustness and has a significant correlation with the existing scoring systems, allowing for classification of the existing data. Furthermore, this data will be used to further develop in silico approaches to assessing human health endpoints (Charmeau-Genevois et al. 2021a Charmeau-Genevois et al. 2021b).

**3Rs Benefit**

The project will refine current animal use by decreasing the number of endpoints that need to be assessed. This data will be used to develop in silico models, with the goal of replacing animal test methods for assessing chemical hazard data.

Animal models, in particular the F-344 rat show limitations for hazard assessment of certain types of hydrocarbons (i.e. waxes). This has been the subject of the regulatory assessment over the past 30 years where studies of different designs have been conducted to elucidate the unique response of the F-344 rat in comparison to the human situation. The lack of relevance of the F-344 rat as an animal model was demonstrated by linking chemical composition of the test substance to an AOP (Adverse Outcome Pathway), explaining the mechanism of action unique to the F-344, which is not relevant to humans. The use of an AOP has shown its usefulness in organising and evaluating the relevance of animal data for human hazard assessment (Carrillo et al. 2021).

**3Rs Benefit**

This project demonstrates the utility of an AOP in evaluating human hazard assessment and human relevance of effects seen in animals. This will allow for a better understanding of chemical mechanism of action, reducing the number of animal tests that need to be performed.
DISSEMINATE AND DISCUSS

To further establish replacement, reduction and refinement of animal use in assessing chemical safety, Shell publishes the results of research and development programs, presents data and ideas in professional forums and engages with regulators, contract research organisations and academia. By doing so, Shell aims to instil a culture of care at the highest scientific and practical level among stakeholders. It also seeks to gather feedback and promote an exchange of ideas that will generate a wide acceptance of Shell’s activities around the 3Rs.

Improved hazard assessment for toxicological endpoints

Shell has continued to work and publish on wider projects that have the potential to lead to wider animal benefits by the refinement of data interpretation, model development, risk assessments and other procedures using vertebrates for regulatory application, such as:

- Prenatal developmental toxicity studies on fumes from oxidised asphalt (OA) in the rat (Boogaard et al. 2021)
- Key event-informed risk models for benzene-induced acute myeloid leukaemia (North et al. 2021)
- A reproductive and developmental toxicity screening study of 1,3-butadiene in Sprague-Dawley rats (Marty et al. 2021)
- Realising the 3Rs potential of non-mammalian models for DART testing (Rooseboom 2021)
SHELL’S USE OF ANIMALS FOR TESTING IN 2021

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.

Table 1 shows the total number of laboratory animals used in procedures from 2017-2021. For 2021, the total number of vertebrates (including mammalian and fish species) was 27,544. This number is a significant decrease in animals reported in previous years. In 2021, most of the vertebrate use occurred because of regulatory compliance and regulatory mandated effluent testing in North America remained the most significant driver in the total number of animals used by Shell.

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<tr>
<td>Rodents</td>
<td>JVs</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Rabbits</td>
<td>Shell</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>3,178</td>
<td>1,214</td>
</tr>
<tr>
<td>Rabbits</td>
<td>Industry consortia</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>3,178</td>
<td>1,214</td>
</tr>
<tr>
<td>Rabbits</td>
<td>JVs</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Birds</td>
<td>Shell</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Animals used</td>
<td>Total</td>
<td>36,459</td>
<td>37,689</td>
<td>37,354</td>
<td>40,121</td>
<td>27,544</td>
</tr>
</tbody>
</table>

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 are reported under industry consortia.
In 2021, more than 95% of all mammalian testing was conducted through industry consortia. The benefit of performing animal testing through consortia is that duplication of tests is avoided and thereby a reduction in total animal use across industry. Standardisation can also produce opportunities for read-across approaches that fill data gaps and suggest further ways to reduce animal testing within substance groupings.

Although Shell reports animal numbers on a 100% basis, the 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 3,416 mammals used in consortia, the Shell share was around 12% of the total number of animals used. This demonstrates how working in consortia helps reduce total animal use across industry.

Table 2 Mammalian species used in consortia for testing

<table>
<thead>
<tr>
<th>Species</th>
<th>Total number</th>
<th>Number used in consortia</th>
<th>“Shell share” of animals used in consortia*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rodents</td>
<td>2,292</td>
<td>2,202</td>
<td>382</td>
</tr>
<tr>
<td>Rabbits</td>
<td>1,214</td>
<td>1,214</td>
<td>44</td>
</tr>
<tr>
<td>TOTAL</td>
<td>3,506</td>
<td>3,416</td>
<td>426</td>
</tr>
</tbody>
</table>

*Calculated based on 6 consortia where Shell is active.
Number of members range from 3-41 companies.

Purpose of testing on animals in 2021

Shell indicates the purpose for animal testing using the categories “3Rs and research and development” (3Rs & R&D Projects) and “regulatory compliance”. The latter includes data that is generated as a regulatory requirement. The purpose of 3Rs and research is defined as data that is generated to understand the human health and environmental hazards of a product and not collected for regulatory reasons, and/or is developed for research intended to advance the 3Rs. This may include the generation of detailed information on the mechanism of toxicity. Understanding the mechanism of action can inform the relevance of the applicable animal model for human risk assessment or help the development of novel non-animal testing methods.

Shell applies targeted and combinatorial testing strategies because it uses the 3Rs concepts to promote animal welfare. 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 animals used. This research project would typically generate data to advance 3Rs methodologies or enhance the information on Shell’s chemical portfolio. Shell also participates in alternative research that will help develop models to help eliminate the need for animal testing. For example, the in vitro data generated in the Simplified Irritation Index project will be used to further refine and validate in silico models, such as the iSafeRat model.

As shown in Figure 1, since 2010 the number of mammals used for projects on 3Rs and research has remained stable. While there were a small number of mammals used for 3Rs and research (90) in 2021, there has been a downward trend in the number of animals used for 3Rs and research, which is connected to Shells goals in developing and adopting non-animal test methods. In comparison, the number
of animals required for regulatory compliance fluctuates from year to year. This is due to changing regulatory demands, affected by updated or new global regulations coming into force.

**Figure 1.** Testing in mammalian species from 2010-2021 by purpose

As indicated earlier, Shell sometimes conducts animal testing for research purposes to understand the health and environmental hazards of a product when testing is not mandated for regulatory compliance. Research data are also used or generated to advance 3Rs methods. The data obtained may include detailed information on the mechanism of toxic action that can inform assessments of the relevance of animal models currently used for human risk assessment. This type of data can also be used to group chemicals into “categories” and by doing so minimise the mandated tests that would otherwise be required for each individual member of the category that may be lacking in vivo data. Since 2010, 3R’s and research activities have resulted in 16% of the total use of mammalian species.

From 2010, when REACH came into effect, to 2021, 82% of all mammals used in regulatory compliance tests worldwide were used solely to comply with REACH (figure 2). This value has decreased slightly from 87% last year but is subject to year-to-year fluctuations (figure 1). Other regulatory frameworks (eg. US) also require the testing on mammalian species, but over the last decade the number of animals is significantly lower (2%) compared to REACH.

**Figure 2.** Overview mammalian species used in chemical testing from 2010-21 and the impact of REACH compared to other non-EU regulatory frameworks and Shell’s 3Rs and research projects
Testing in fish

In 2021, no fish were used worldwide for 3Rs development activities or for internal research purposes, although fish were the vertebrates most used for regulatory compliance (86%) (figure 4).

Overall fish numbers decreased from the 2020 data by about 25%. This was driven by the completion in May 2020 of a 2-year joint industry study required under the discharge permit for offshore facilities in the Gulf of Mexico. The effluent study was performed through a consortium of 33 different operators in the Gulf of Mexico to support compliance of operations.

Most of the non-mammal-vertebrate testing in 2021 stemmed from fish testing that was directly required under regulations relating to whole effluent toxicity assessment (table 3). The primary driver for Shell’s fish use, accounting for 100% of all fish used in 2021, remains whole effluent toxicity testing requirements for discharge permits in North America and hazardous waste disposal in California. This has been the trend since 2015, where >90% of the tests on fish have been related to regulatory compliance (figure 3).

Table 3. Fish numbers and purpose, 2015 – 2021

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>3Rs and Research*</td>
<td>18,589</td>
<td>8,480</td>
<td>274</td>
<td>0</td>
<td>450</td>
<td>106</td>
<td>0</td>
</tr>
<tr>
<td>Regulatory Compliance</td>
<td>66,867</td>
<td>46,871</td>
<td>34,378</td>
<td>36,819</td>
<td>36,130</td>
<td>31,870</td>
<td>24,038</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>85,456</strong></td>
<td><strong>55,351</strong></td>
<td><strong>34,652</strong></td>
<td><strong>36,819</strong></td>
<td><strong>36,580</strong></td>
<td><strong>31,976</strong></td>
<td><strong>24,038</strong></td>
</tr>
</tbody>
</table>

*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 testing is also performed to help Shell understand the potential implications of anticipated future regulatory requirements or applications for new permits (discharges).
Conclusions
For 2021, regulatory compliance is the main driving force for conducting tests on mammals (EU REACH) and fish (North America), as shown in Figure 1 and Table 3 for 2021.

The use of fish for regulatory mandated effluent testing in North America remains the most significant contributor to the total number of animals used by Shell, although numbers have decreased due to the selling of assets in the USA. However, Shell will continue to focus on promoting 3Rs methodologies likely to be accepted by regulators. Over the past 10 years, EU-REACH has been the main regulatory framework demanding tests on vertebrate species. Although the numbers had been stable since 2016, we saw a significant increase in 2020 because of increasingly animal-intensive study requests under the REACH information requirements. At the end of 2020, European Chemicals Agency (ECHA) required more testing for systemic, reproductive and developmental toxicity endpoints. Regulatory determination of developmental toxicity requires testing in a rodent species and often also testing in a non-rodent species may be required and the second species commonly used is the rabbit. Some of these animal-intensive studies were completed by Shell in 2021 and are reported here, while some ongoing studies completed in 2022 will be reported in 2023. Thus, for next year we expect to see an increase in the number of rodent and rabbits used for REACH regulatory compliance. In the face of increased regulatory pressure in the coming years, there may be an increase in animal use; in these situations, Shell will look to work with animal laboratories to refine animal welfare practices (e.g., animal husbandry and care) and reduce discomfort. Shell will continue to maintain regulatory compliance while striving to be transparent around our actions to reduce animal use for regulatory compliance by using the best science available.
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. The external Panel was established to provide independent scrutiny of, and support for, Shell’s activities in this area.

Terms Of Reference Of The Panel

Shell invites individual Panel members 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 2021

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 serving as chair of two scientific committees – Emerging and Newly Identified Health Risks; and Toxicity, Ecotoxicity and the Environment – and being a member of several working groups on future risk assessment methodology that have addressed alternatives to animal testing.

Sarah Wolfensohn OBE FRCVS (Professor of Animal Welfare at the University of Surrey, UK)

Sarah Wolfensohn is a veterinary surgeon, a Royal College of Veterinary Surgeons-recognised specialist in laboratory animal science and a European specialist in animal welfare, ethics and law. While in general practice, she became Named Veterinary Surgeon for a number of small pharmaceutical and biotech companies, before being appointed Head of Veterinary Services at the University of Oxford. She is now Professor of Animal Welfare at the University of Surrey’s veterinary school and also runs an independent consultancy on animal health and welfare. She has published textbooks and numerous papers in the area of animal science and welfare, and is a member of the UK government’s Animal Welfare Committee. She was previously a member of the UK Animals in Science Committee and the Animal Procedures Committee, and was closely involved in the UK government’s development of its Animal Health and Welfare Strategy. She has served on several international committees and working groups that seek to refine animal use and improve welfare.

John P. Giesy (University Distinguished Professor of Environmental Toxicology, University of Saskatchewan, Saskatoon, Canada)

John P. Giesy, a dual citizen of Canada and the USA, is an ecotoxicologist and environmental chemist who has developed laboratory and field methods to assess risks of chemical to humans and wildlife. He has pioneered, molecular and in vitro techniques as well as quantitative structure activity models to supplement in vivo studies and was a member of the US EPA Endocrine Disruptor and Screening Committee. He has served as an advisor to local,
Troy Seidle (Vice President of Research & Toxicology, Humane Society International)
As Humane Society International vice president of research and toxicology, Troy Seidle leads a global science and public policy team that works to promote a new paradigm in toxicology and health research based on approaches rooted in human biology. He possesses more than two decades’ experience in biomedical and toxicological science policy, and specialist knowledge of emerging tools of predictive biology, legal and regulatory frameworks across numerous countries and sectors, and a drive to find collaborative solutions to complex challenges. Troy currently serves on the animal welfare panel of Shell, and on the Canadian Council on Animal Care subcommittee on ethics, and in the past has served on expert groups for the OECD, European Union, US EPA, Health Canada, the New Zealand Ministry of Health, and others.
REFERENCES


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