IFSCC 2025 full paper (IFSCC2025-1262)

Next Generation Risk Assessment of Octane-1,2-diol

Kirsten Gerloff[a*], Matthew Dent[b], Steve Gutsell[b], Ans Punt[b], Jens Schlirf[c], Peter Griem[a]

[a]Symrise AG, Muehlenfeldstrasse 1, 37603 Holzminden, Germany
[b]Unilever, Colworth Science Park, Bedford, MK44 1LQ, United Kingdom
[c]SCC Scientific Consulting Company, Am Grenzgraben 11, 55545 Bad Kreuznach, Germany
*Corresponding author, Kirsten.gerloff@symrise.com, Phone +49 5531 90 3793

1. Introduction

Since animal testing has been banned for cosmetics and their ingredients in the EU in 2013, the development of the concept of Next Generation Risk Assessment, or NGRA, for the cosmetics sector has evolved. An NGRA is an exposure-led, hypothesis driven risk assessment approach that incorporates one or more New Approach Methodologies (NAMs) to protect against harm from chemical exposures, without reliance on animal experiments [1]. Therefore, the use of NAMs has become vital for the cosmetics industry and developments in this field have advanced quickly. NAMs include not only *in vitro* methods, but also in silico, ex vivo and in chemico methods as well as grouping and read across approaches. NGRA is an emerging tool for integrating a variety of NAMs data from different sources to develop a comprehensive picture of consumer or, more recently, worker safety in the absence of single *in vitro* replacement methods for more complex endpoints, such as systemic and developmental toxicity. In principle, all available bioactivity data are evaluated to derive the Point of Departure (PoD, usually an *in vitro* concentration), which is then compared to consumer or, as demonstrated in our study, worker internal exposure, e.g., plasma concentration, resulting in the Bioactivity Exposure Ratio (BER) [2]. The PoD indicates the lowest concentration at which any kind of biological response to the tested substance occurs. Recently, the European Chemicals Agency (ECHA) has issued a request for extensive animal developmental and reprotoxicity data for Octane-1,2-diol. The major concern triggering the request for an OECD TG 443 study was a lower birth weight of fetuses from a maternal dose of 1000 mg/kg bw/day in a rat teratogenicity toxicity study (OECD TG 414, PNDT). Since the subject of protection for ECHA are both workers and the environment, the animal testing ban for cosmetics is not applicable. Although they should officially be applied as a “last resort” only, requests for animal testing are still considered a common requirement [3].

To avoid further animal testing, we aimed to investigate the cause of the lower birth weight that triggered the request for the OECD TG 443. We studied possible underlying developmental toxicity mechanisms and developed an NGRA to investigate safe use of Octane-1,2-diol for workers. Potential primary developmental toxicity effects were explored by using two well-established *in vitro* developmental toxicity studies, namely the *devTox quickPredict* and the *ReproTracker* assay. Both assays use human induced pluripotent stem cells (HiPSCs) and screen for different markers of perturbed embryonic development, and the combination of these assays alongside *in vitro* pharmacological profiling, toxicogenomics and cell stress assays provides broad coverage for potential developmental and reproductive toxicity [2]. Neither the HiPSC assays nor the broader screening tools indicated any DART liabilities following treatment with Octane-1,2-diol. Therefore, we hypothesized that the low birth weight was caused by mechanisms other than primary developmental toxicity effects.

Reports indicate that diols, including Octane-1,2-diol, may have antimicrobial properties [4, 5]. Recently, the role of the gut microbiome in diverse aspects of fetal development is gaining increasing attention and recognition [6-8]. A multitude of adverse effects to the offspring were reported to be caused by perturbation of the normal healthy gut microbiome including effects on the immune system, brain development, development of allergic disorders, and preterm births or miscarriages. This gave rise to the hypothesis that the microbiome also plays a role in the effects found previously in rat fetuses which triggered further animal testing requests by the ECHA.

The goal for the current work was to assess whether performing an OECD TG 443 is necessary to confirm that occupational exposure to Octane-1,2-diol will not cause reproductive/developmental toxicity or whether this could be answered in an animal free test assessment. The developed NGRA followed the same framework that is already increasingly used for the safety evaluation of cosmetic products, and the applicability of this system to the worker could be demonstrated. Relevant exposure scenarios throughout the production chain of Octane-1,2-diol were assessed to ensure that all possible risks arising from the handling of Octane-1,2-diol in our production and supply chain are controlled at an acceptable level.

2. Materials and Methods

Exposure Assessment

The life cycle of Octane-1,2-diol in our production and supply chain was mapped out in detail. The highest exposure values were selected for each contributing exposure scenario during manufacturing, formulation of compounds and end products, as well as during professional use by using the highest cumulative exposure values via the dermal and inhalation route.

Inhalative exposure was calculated using ART (Advanced Reach Tool), predicting air concentrations in a worker's personal breathing zone without any personal respiratory protection equipment. Dermal exposure (long-term, systemic) was calculated using ECETOC TRA Workers exposure tool. The tools' outputs provide estimates of air concentration and dermal deposition for specific contributing scenarios that arise during a series of events ('exposure scenarios') based on Process Categories (PROCs) defined under REACH. For the assessment, all exposure routes were considered, with direct exposure being the only source.

Physiologically Based Kinetic (PBK) modelling

A PBK model is a structural mathematical model, comprising the tissues and organs of the body connected via the blood circulatory system. The principal application of PBK models is the prediction of target tissue or plasma concentrations of the parent chemical and/or its metabolites. PBK modelling and simulations were conducted using GastroPlus 10.1 (Simulation Plus, Lancaster, CA, USA). The PBK model can be used to simulate internal exposure in humans after inhalation and dermal exposure using the outcome of standard REACH exposure tools. To this end, the oral and inhalation exposure were combined to one dose for the exposure duration of a typical 8-hour work shift. The predicted peak plasma concentration allowed risk characterization through the calculation of a BER.

Dermal and inhalation exposure estimates of all relevant PROCs were used to calculate the expected resulting maximum peak concentration (C_{max}) in a 60 kg healthy individual. All activities from manufacture, formulation, and professional use are covered.

To understand and quantify population variability and parameter uncertainty, probabilistic PBK modelling was conducted to estimate the range of biologically plausible exposures (i.e., plasma C_{max}). This was achieved through a Monte-Carlo simulation of 1000 subjects (the 'population simulation' function in GastroPlus) by considering the inter-individual variability, a virtual European population, with a focus on the working population (age ranged 18 to 65 years, and weight range 80 to 120 % of typical weight, 50% female). As output, statistical distributions (median and 5th and 95th percentiles) were generated for plasma C_{max}. A second working population simulation (N=1000) was performed for a pregnant female population (age range 18 to 45 years, weight range 80 to 120 % of typical weight, gestational age 1 to 38 weeks).

Bioactivity Assessment

A large suite of *in vitro* methods was used to perform a bioactivity assessment using human cell lines with the goal to derive a PoD from a battery of assays with a broad biological coverage. All PoDs were derived as reported previously [9, 10].

In vitro pharmacology profiling

In vitro pharmacology profiling (IPP) has been performed to screen for specific and high affinity non-covalent binding interactions with various targets, many of which have been associated with DART liabilities. A total of 73 molecular targets were evaluated including pharmacologic receptor binding, cellular and nuclear receptor functional assays, enzyme and uptake assays and *in vitro* metabolism assays using a concentration of 100 µM Octane-1,2-diol. Stimulation or inhibition of more than 50% of the maximal response was considered effective.

Toxicogenomics

Alterations in gene expression can be indicative of an adaptive or adverse response to a potential stressor. A toxicogenomics assessment was conducted upon treatment with Octane-1,2-diol to analyze responses in RNA transcription across the genome and to therefore enable a sensitive measurement of possible biological effects. For broad biological coverage three cell models were used (HepG2, HepaRG, and MCF-7 cell lines) and first screened for cytotoxic

effects of Octane-1,2-diol. Following the confirmation of the absence of cytotoxicity at up to 5 mM, a total of 7 doses (0.32-5000 µM dose-range) was tested per cell line in the main study.

In vitro Cell Stress Panel

Cellular stress pathways were analyzed through 36 biomarkers representing 12 key stress mechanisms including cellular stress signaling pathways, organelle health, cellular cytotoxicity, mitochondrial toxicity, inflammation and general cell health. Octane-1,2-diol was tested at 8 concentrations ranging from 0.305-5000 µM over a treatment period of 24 hours.

Human induced pluripotent stem cell (HiPSC) models

To complement the IPP, toxicogenomics and cell stress panel and widen the DART coverage of the assessment, two HiPSC models we used.

DevTOXquickPredict

Octane-1,2-diol was tested in the human induced pluripotent stem cell (hiPSC)-based devTOX quickPredict assay. HiPSCs were exposed to Octane-1,2-diol for a period of 48 hours. The cells were then analyzed for the metabolic perturbation of two biomarkers, ornithine and cystine, in a ratio (o/c ratio) to identify the concentration at which a test article shows developmental toxicity potential. PoDs were calculated from the respective dose response curves as described in [9].

Reprotracker

The ReproTracker assay uses hiPSCs that were differentiated into specific cell types, cardiomyocytes, hepatocytes and neural rosettes. Cells were treated with Octane-1,2-diol for periods of up to 21 days. Cells were then monitored for alterations in expression pattern of the tissue-specific biomarkers and cell morphology.

BER calculation

The Bioactivity-exposure ratio, or BER, is derived by calculating the ratio of the nominal concentration of the PoD to the relevant plasma C_{max} estimate from the PBK modelling for the exposure scenario contributing the highest calculated exposure [2].

Microbiome studies

The intestinal bacterial species *Blautia producta, Butyrivibrio fibrisolvens, Escherichia coli* and *Intestinimonas butyriciproducens*, selected for the *in vitro* tests were ordered from the German Collection of Microorganisms and Cell Cultures (DSMZ). The respective strains were each incubated with 5 different concentrations of Octane-1,2-diol (0.13 to 1 %) for 24 to 72 h, depending on the strain and growth conditions. The minimal inhibitory concentration (MIC) was defined as the Octane-1,2-diol concentration at which less than 10 % bacterial growth was observed (=MIC/90).

3. Results and discussion

The exposure calculations revealed that the highest internal plasma concentrations corresponded to the exposure scenarios “material transfer at non-dedicated facilities, equipment cleaning and maintenance” (PROC 8a) and “Transfer into small containers” (PROC 9) of Formulation scenario 2 as well as “Spraying of a professional cleaning and maintenance

product", PROC 11 of the scenario "Professional use". Table 1 describes all relevant exposure scenarios with the respective PROCs and resulting dermal and inhalation exposure values that were used for further assessment.

Exposure scenario	PROC Number	Process description	Dermal Exposure estimates (mg/kg bw/day)	Inhalation Exposure estimates (mg/m3)
Manufacture	PROC 1	Chemical production or refinery in closed process without likelihood of exposure or processes with equivalent containment	1.70E-03	1.20E-01
	PROC 8a	Transfer of substance or mixture (charging and discharging) at non-	6.86E-01	2.90E-01
	PROC 9	Transfer of substance or mixture into small containers (dedicated filling line, including weighing)	3.43E-01	2.90E-01
	PROC 15	Use as laboratory agent	1.70E-02	1.00E-01
Formulation scenario 1	PROC 4	Use in batch and or other process (synthesis) where opportunity for	3.43E-01	5.40E-05
	PROC 9	Transfer of substance or preparation into small containers (dedicated filling line, including weighing)	3.43E-01	5.30E-03
Formulation scenario 2	PROC 1	Storage (Closed process)	6.80E-03	1.30E-03
	PROC 3	Mixing operations (closed systems) in batch process including filling of equipment and sample collection	3.40E-02	1.30E+00
	PROC 5	Mixing operations (open system) in batch process including filling of equipment and sample collection	6.86E-01	2.70E+00
	PROC 8a	Material transfers from/to vessel/container at non-dedicated facility, equipment cleaning and maintenance	6.86E-01	3.10E+00
	PROC 9	Transfer into small containers	6.86E-01	3.10E+00
	PROC 14	Tabletting, compression etc.	6.86E-01	4.30E-02
	PROC 15	Laboratory reagent	6.80E-02	1.00E+00
Professional use (cleaning)	PROC 1	Using a diluted professional cleaning solution or maintenance product in a closed cleaning equipment	6.80E-04	4.10E-04
	PROC 2	Using a diluted professional cleaning solution in a semi closed cleaning equipment	2.70E-02	7.40E-04
	PROC 4	Using a diluted professional cleaning solution or maintenance product in a cleaning equipment; opportunity for exposure arises	1.37E-01	7.30E-04
	PROC 8a	Transfer of professional cleaning or maintenance product (charging/discharging) to a cleaning equipment (machine/vessel/bucket)	2.74E-01	6.70E-03
	PROC 8b	Transfer of professional cleaning or maintenance product (charging/discharging) to a dedicated cleaning equipment	2.74E-01	6.70E-03
	PROC 10	Brushing a professional cleaning or maintenance product	5.49E-01	7.40E-02
	PROC 11	Spraying of a professional cleaning or maintenance product	1.07E+00	3.90E-01
	PROC 13	Professional Use of Drain Blockers & Treatment of articles by dipping or pouring with a professional cleaning or maintenance product	2.74E-01	7.50E-04

Table 1: Relevant process categories (PROCs), their description and corresponding dermal and inhalative exposure.

In vitro to *in vivo* extrapolation by PBK modelling resulted in an overall blood plasma concentration of 2.1 µM of Octane-1,2-diol for a model 60 kg non-pregnant female for each of PROC 8a, PROC 9 and PROC 11, therefore this value is considered the highest internal concentration that can be reached in a worker being exposed to Octane-1,2-diol throughout a whole 8-hour shift without local exhaust ventilation or any personal protection equipment except for gloves. All other activities leading to Octane-1,2-diol exposure resulted in substantially lower plasma concentrations. The *in vitro* tests related to developmental toxicity did not reveal any effect, neither did the *in vitro* pharmacology profiling. Biological effects were found as transcriptomic changes in all three cell lines across the tested concentration range and the cell stress assay, resulting in a PoD of 48.9 µM, as depicted in Figure 1. This PoD is not intended to describe a specific adverse outcome or pathology but rather aims to be

protective of human health, as this approach estimates the exposure concentration at which no biological response is expected [11, 12].

Assay	tested cell type	analysis method	PoD
HTTr	HepaRG	bifrost	103.9
	HepG2		108.8
	MCF-7		**48.9**
	HepaRG	minbmd	259. 3
	HepG2		1029.2
	MCF-7		968.9
Cell stress	HepG2	bifrost	272.3
IPP			no effect
DevTox	hiPSC		no effect
Reprotracker	hiPSC		no effect

Figure 1: Overview of the points of departures of the analyzed *in vitro* endpoints

This PoD-value was used to derive the BER in the next step, in which both exposure estimates (C_{max}) and the most sensitive endpoint were used for calculation as described in [2]. With the calculated plasma C_{max} Octane-1,2-diol for a combined inhalative and dermal occupational exposure being 2.1 µM, the resulting BER is 48.9/2.1 = 23.3.
Considering population variability and parameter uncertainty, probabilistic PBK modelling was performed for non-pregnant and pregnant workers and professional users as described above. The resulting BERs based on the 5th and 95th percentiles and the BERs for the highest exposure concentrations of the other two exposure scenarios are depicted in Table 2. For comparison, C_{max} and corresponding BER calculations are additionally shown for a model 60 kg non-pregnant female during manufacture and formulation scenario 1.

		Cmax (µM)	BER
Worker formulation scenario 2, PROC 8a and 9	non-pregnant	2.3 (1.7-3.1)	21.3 (15.8-28.8)
	pregnant	2 (1.9-2)	24.5 (24.5-25.7)
Professional use, PROC 11	non-pregnant	2.3 (1.7-3)	21.3 (16.3-28.8)
	pregnant	1.9 (1.9-2)	25.7 (24.5-25.7)
Worker manufacture		1.37	35.7
Worker formulation scenario 1		0.64	76.4

Table 2: Bioactivity exposure ratios (BERs) of all calculated occupational exposure scenarios and the respective C_{max} values used for BER calculation.

To determine the concentration at which Octane-1,2-diol induces toxicity to relevant intestinal bacteria, the *in vitro* microbiome study was performed. With this, we might explain the reduced birth weight seen in a previously performed *in vivo* study that triggered the additional animal test by ECHA.

The *in vitro* microbiome study revealed that the concentration at which Octane-1,2-diol induces a marked decrease in bacterial viability of relevant intestinal bacteria was 0.25 % Octane-1,2-diol, corresponding to a local concentration of 2.5 mg/ml, as shown in Figure 2.

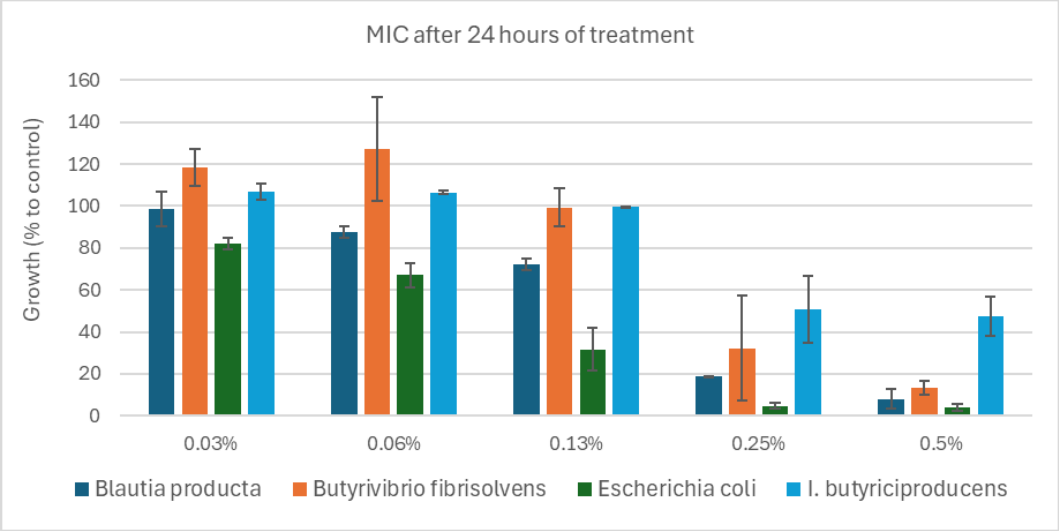

Figure 2: MIC of B. producta (A), B. fibrisolvens (B), E. coli (C) and I. butyriciproducens (D). The strains were inoculated to an OD600 of 0.1 and incubated with different concentrations (v/v) of Octane-1,2-diol under strictly anaerobic conditions at 37°C for 24 h. The growth was determined by measuring OD600 in a plate reader (TECAN Infinite 200 Pro M-Series). The MIC/90 is the concentration at which less than 10 % growth was observed. N=2 or 3 (E. Coli)

Based on this, an intestinal concentration of 0.25% was chosen to simulate in a PBK model how much Octane-1,2-diol a rat, or a human, would need to orally ingest to reach this concentration in the various intestinal compartments. As rats had access to food ad libitum during the course of the teratogenicity *in vivo* study, we simulated the required amounts of Octane-1,2-diol both in the fed and the fasted state. The results are shown in Figure 3.

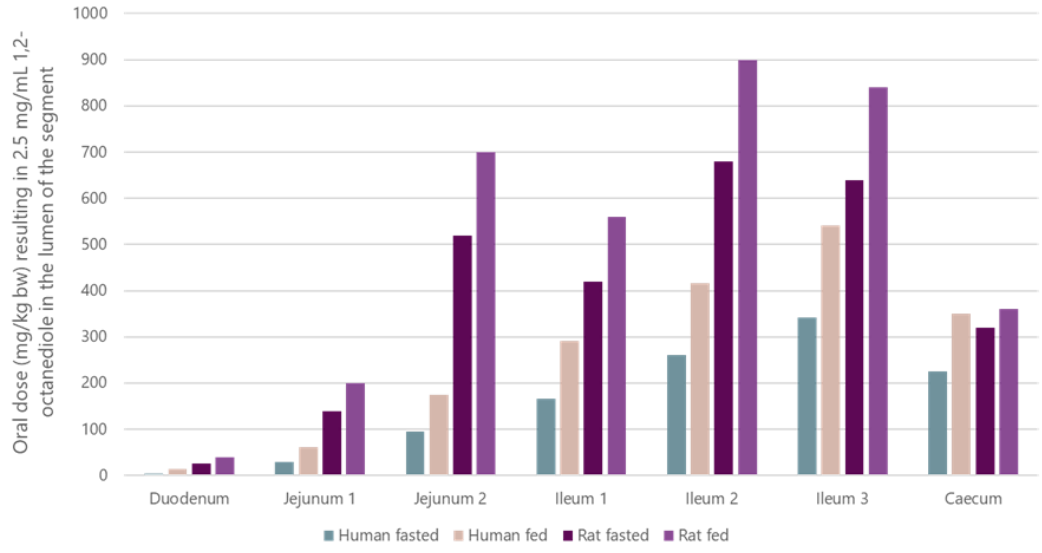

Figure 3: Required doses to reach a concentration of 2.5 mg/ml (equals 0.25%) of Octane-1,2-diol in the respective intestinal compartments of the fed or fasted rat and human.

In the fed rat, an oral dose between 200-900 mg/kg bw would result in an Octane-1,2-diol-concentration of 0.25 % in the respective intestinal section (small and large intestine).

4. Discussion

The resulting BERs were found to be in an overall range of 21.3-76.6, with confidence intervals starting from 15.8. BERs for pregnant populations were overall found to be in similar ranges than in non-pregnant workers. Middleton and colleagues described a decision model for defining the level of complexity of a PBK model [10]. According to this, the developed PBK model for Octane-1,2-diol is a Level 2 model, as it incorporates both *in silico* and *in vitro* values. The resulting decision model concludes that overall, the risk for the exposed user can therefore be considered low if the BER exceeds 11. Here, we found that all calculated exposure scenarios clearly exceeded this evaluation level, even when accounted for intraindividual variation.

None of the *in vitro* tests related to developmental toxicity revealed any effect, therefore the reduced birth weight seen in the existing OECD TG 414 study might be explained by a secondary mechanism. There is increasing evidence that a perturbed gut microbiome, for instance by oral uptake of antibiotics, can cause a reduction in birth weight in humans with an increased risk of around 11 % (low birth weight was considered as <2500 g in this study) [13] or average lower birth weights of 138 g [14]. More recently it was suggested that a microbiome perturbation in the late second trimester specifically is associated with reduced birth weight [15]. Similar effects have also been described in mice, where alteration of the intestinal microbiota composition by maternal antibiotic treatment starting from gestational day 15 resulted in a significant reduction in birth weight, with even stronger effects seen on postnatal day 7 [16]. But not only maternal, also paternal antibiotic treatment appeared to affect the birth weight of the offspring. Recently, a study found that after antibiotic treatment of male mice followed by mating with untreated females, offspring had a significantly lower birth weight, and this reduced weight, compared to control F1 animals, remained significant even after 21 days postnatal development along with significantly increased postnatal mortality [17]. The adverse effects were also found upon in vitro fertilization, suggesting that paternally induced F1 phenotypes are transmitted primarily through the gametes and copurifying molecules. This indirect effect on offspring was, however, found to be reversible after 8 weeks of recovery of the treated males.

The calculated effect dose-range of 200-900 mg/kg bw found in our study was within the tested dose range in the *in vivo* study and thus well within the dose range in which a reduced birth weight was noted. Therefore, effects on the microbiome can be expected to have contributed to the reduced birth weight of the fetuses. However, this effect is expected to be reversible upon termination of the treatment, based on current literature.

5. Conclusions

The developed NGRA considered relatively high exposure to Octane-1,2-diol by applying a conservative approach for workers and professional users. All uses can be considered safe, based on a recently developed decision model evaluating the applied PBK model and subsequently derived BERs. Studies on the intestinal bacteria suggest that animals that are exposed to Octan-1,2-diol in relevant *in vivo* testing doses might display a disturbed gut microbiome, which can lead to effects in the offspring. This can explain the effects previously found *in vivo* that triggered a request for additional animal studies. Conducting further animal studies using high oral doses is highly likely to have similar impacts on test organisms due to the reversible disruption of the gut microbiome. These findings would do nothing to inform the safety assessment of Octane-1,2-diol for workers where exposures are via dermal and inhalation and result in much lower systemic exposures. Therefore, our work leads us to believe that no further animal experiments are scientifically necessary nor warranted to ensure worker safety under REACH.

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