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Draft analysis of the most appropriate risk management option (RMOA)

**Substance name: 1,3-diphenylguanidine (DPG)**

**EC number: 203-002-1**

**CAS number: 102-06-7**

**Authority: FR CA (aMSCA)**

**Date: 28.06.2023**

**Cover Note**

*FRANCE CA registered his intention to revise the current Annex VI entry and a dossier proposal for a revised harmonised classification and labelling for DPG is ongoing. In this RMOA, the need for further regulatory action on DPG is investigated. Exposition of this hazardous substance to consumers and workers, and subsequent risk assessment, are analysed. In addition, emissions to water and the conditions of release of DPG into the environment (limit value) are discussed.*

**General Comments and additional relevant information are invited on this RMOA by Month Date Year.**

**Additional specific questions:**

* Do you have further information related to degradation products aniline, N-nitroso-diphenylurea and phenyl guanidine?
* Do you have additional information on the concentration of DPG and/or its degradation products in articles?

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The author does not accept any liability with regard to the use that may be made of the information contained in this document. Usage of the information remains under the sole responsibility of the user. Statements made or information contained in the document are without prejudice to any further regulatory work that ECHA, the Member States or other regulatory agencies may initiate at a later stage. Assessment of regulatory needs and their conclusions are compiled on the basis of available information and may change in light of newly available information or further assessment.

# Foreword

The purpose of the assessment of regulatory needs of a group of substances is to help authorities conclude on the most appropriate way to address the identified concerns for a group of substances or a single substance, i.e. the combination of the regulatory risk management instruments to be used and any intermediate steps, such as data generation, needed to initiate and introduce these regulatory measures.

An assessment of regulatory needs can conclude that regulatory risk management at EU level is required for a (group of) substance(s) (e.g. harmonised classification and labelling, Candidate List inclusion, restriction, other EU legislation) or that no regulatory action is required at EU level. While the assessment is done for a group of substances, the (no) need for regulatory action can be identified for the whole group, a subgroup or for single substance(s).

The assessment of regulatory needs is an important step under ECHA’s Integrated Regulatory Strategy. However, it is voluntary, i.e., it is not part of the processes defined in the legislation but aims to support them.

The assessment of regulatory needs can be applied to any group of substances or single substance, i.e., any type of hazards or uses and regardless of the previous regulatory history or lack of such. It can be done based on different level of information. A Member State or ECHA can carry out this case-by-case analysis. The starting point is available information in the REACH registrations and any other REACH and CLP information. However, more extensive set of information can be available, e.g. assessment done under REACH/CLP or other EU legislation, or can be generated in some cases (e.g. further hazard information under dossier evaluation). Uncertainties associated to the level of information used should be reflected in the documentation. It will be revisited when necessary. For example, after further information is generated and the hazard has been clarified or when new insights on uses are available. It can be revisited by the same or another authority.

The responsibility for the content of this assessment rests with the authority that developed it. It is possible that other authorities do not have the same view and may develop further assessment of regulatory needs. The assessment of regulatory needs does not yet initiate any regulatory process but any authority can consequently do so and should indicate this by appropriate means, such as the Registry of Intentions.

For more information on Assessment of regulatory needs please consult ECHA website[[1]](#footnote-2).

# Glossary

|  |  |
| --- | --- |
| ANSES | *Agence Nationale de Sécurité Sanitaire de l’alimentation, de l’environnement et du travail* [French Agency for Food, Environmental and Occupational Health & Safety] |
| aMSCA | Author member state competent authority |
| CAD | Chemical Agent Directive |
| CCH | Compliance Check |
| CLH | Harmonised classification and labelling |
| CMR | Carcinogenic, mutagenic and/or toxic to reproduction |
| CMRD | Carcinogens, Mutagens or Reprotoxic substances Directive |
| CSR | Chemical safety report |
| Dev | Dossier evaluation |
| DNEL | Derived no effect level |
| DWD | Drinking Water Directive |
| DWTP | Drinking Water Treatment Plant |
| ED | Endocrine disruptor |
| ELT | End of Life Tyres |
| EOGRTS | Extended one-generation reproductive toxicity study |
| ES | Exposure scenario |
| ETRMA | European Tyre & Rubber Manufacturers Association |
| GRG | General rubber goods |
| IED | Industrial emission Directive |
| IOELV | Indicative occupational exposure level value |
| LOAEL/LOAEC | Lowest observed adverse level/concentration |
| MSCA | Member state competent authority |
| NOAEL/NOAEC | No observed adverse level/concentration |
| OEL | Occupational exposure limit |
| OSII or TII | On-site isolated intermediate or transported isolated intermediate |
| PBT/vPvB | Persistent, bioaccumulative and toxic/very persistent and very bioaccumulative |
| PMT | Persistent, mobile in water and toxic |
| PND | post-natal day |
| PROC | Process category |
| RCR | Risk characterisation ratio |
| REACH | Regulation (EC) No 1907/206 of 18/12/06 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) |
| RMOA | Regulatory management options analysis |
| RMM | Risk Mitigation Measure |
| RRM | Regulatory risk management |
| SCOEL | Scientific Committee on Occupational Exposure Limits |
| SEv | Substance evaluation |
| STOT RE | Specific target organ toxicity, repeated exposure |
| STP | Sewage treatment plant |
| SVHC | Substance of very high concern |
| WFD | Water framework directive |
| WWTP | Waste Water Treatment Plant |

# Overview of the substance

DPG is mainly used in the manufacture of rubber as a vulcanizing agent and vulcanizing accelerator. This substance is used in polymers, for the manufacture of general rubber goods (flooring, foot wear, toys) and the manufacture of tyres. End of life tyres (ELT) can be transformed and used in articles like synthetic turf field and shock absorbing tiles. Literature also reported the presence of DPG in articles such as medical gloves (Hamnerius *et al*., 2014, Crepy *et al*., 2016).

1,3-diphenylguanidine (DPG) was included in the list of substances in the CoRAP (Community Rolling Action Plan) in 2012 on the grounds of suspected CMR (genotoxic potential), high RCR (risk characterisation ratio), and high aggregated tonnage. The evaluation was taken in charge by France and other concerns were identified during the evaluation. The additional concerns were reproductive toxicity, skin sensitisation, environmental fate, exposure of environment, and other hazard/risk-based concerns, i.e. composition of the substance as regards to impurities such as aniline or nitrosamines formed during processes involving high temperature conditions.

During substance evaluation, a data gap was identified for this substance according to REACH annex X, section 8.7.3 covering adverse effects on the full range of reproductive endpoints. A decision on compliance check under REACH regulation was sent to the Registrants on March 2019 by ECHA to request an OECD TG 443 study (EOGRTS), which results were submitted in July 2021.

The substance evaluation conclusion report was published in December 2020 (ANSES, 2020). It was concluded that a revision of the harmonised classification is necessary. In particular, a proposal for classification for reproductive toxicity should be considered after assessment of the EOGRTS study. For the environmental risk characterisation, FR CA concluded to “a lack of reliable information regarding the emission levels linked to some stages of the DPG life cycle. This situation does not allow to carry out a comprehensive and realistic risk assessment for the registered substance.” In addition, the necessity to limit emission in the environment needs to be further discussed. For the workers and consumers risk characterisation, the conclusion were provisional. FR CA noted that it should be clarified whether DPG poses a realistic risk to workers, and whether further risk management measures are necessary in order to protect the consumers and workers, pending the reception of the EOGRTS study. Risks related to by-products formed during vulcanization were characterised for aniline as the sole degradation product. No risk was identified in the conclusion document on this basis. However, uncertainties remained after the assessment regarding by-products because no additional information was available for the two other by-products mentioned by the Registrants (N-nitroso-diphenylurea and phenyl guanidine) and these substances are not registered under REACH.

Therefore, it was concluded that follow-up regulatory action at EU level needed to be discussed in a RMOA.

This RMOA focus on the consideration of the recent EOGRTS for DNEL derivation and for the assessment of possible endocrine disrupting properties (see Annex I section 2.1). It also aims at revising and refining risk characterisation for human health and for the environment and to discuss the need to set RMM to address risks related to the use of DPG and the formation of degradation products.

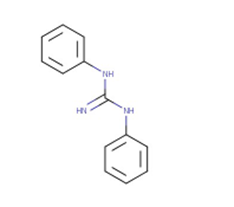
## Substance identifiers

Table 1: Substance identity

|  |  |
| --- | --- |
| **SUBSTANCE IDENTITY** | |
| **Public name :** | 1,3-diphenylguanidine |
| **EC number:** | 203-002-1 |
| **CAS number:** | 102-06-7 |
| **IUPAC name (public):** | 1,3-diphenylguanidine |
| **Index number in Annex VI of the CLP Regulation:** | 612-149-00-4 |
| **Molecular formula:** | C13H13N3 |
| **Molecular weight or molecular weight range:** | 211 g/mol |
| **Synonyms:** | *trade names:*  *DPG*  *DENAX*  *GUANIDINE, N,N’-DIPHENYLtrade*  *DFG*  *GUANIDINE, 1,3-DIPHENYLtrade*  *MELANILINE*  *N,N’-DIPHENYLGUANIDIN*  *SYM-DIPHENYLGUANIDINE*  *VULKAZIT*  *1,3-DIPHENYLGUANIDINE*  *Vulkacit D*  *EKALAND DPG*  *MIXLAND+ DPG* |

**Type of substance**  Mono-constituent  Multi-constituent  UVCB

**Structural formula:**

****

Additional physical-chemical properties of DPG can be found in Annex I, section 3.2.3, table 24.

## Completed or ongoing process

**Table 2: Processes identified for substance 1,3-diphenylguanidine**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **EC/List number** | **Other REACH related work** | **RMOA** | **Evaluation** | | | **Authorisation** | | **Restriction** | **CLH** | **Other processes/ EU legislation** |
| **CCH** | **TPE** | **SEV** | **Candidate List** | **Annex XIV** | **Annex XVII** | **Annex VI (CLP)** |

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 203-002-1 |  |  | X | X | X |  |  |  | X | see further details below |

Data consulted on March 2023

The dossier and substance evaluation processes have been completed. The requested information regarding compliance checks and testing proposals have been submitted by the Registrants.

1,3-diphenylguanidine (DPG) has an harmonised classification under regulation (EC) no. 1272/2008 on classification, labelling and packaging of substances and mixture at European level (CLP regulation). Following the substance evaluation conclusion report (ANSES, 2020), it was concluded that a revision of the harmonised classification is needed. This revision is ongoing and an overview of the current classification and new proposal is presented in section 1.4.1.

Based on its current classification, 1,3-diphenylguanidine may be concerned by other regulations due to its presence in the Annex VI of the CLP regulation (ECHA disseminated database[[2]](#footnote-3)):

1. Active implantable medical device directive
2. Directive Chemical Agent Directive “CAD” (directive 98/24/EC on the protection of the health and safety of workers from the risk related to chemical agents at work)
3. Construction product regulation
4. Cosmetic product regulation
5. EU ecolabel regulation
6. End of life vehicle directive
7. Food contact material: not allowed for use
8. General product safety directive
9. In Vitro Diagnostic Medical Devices Directive
10. Marine environmental policy framework directive
11. Medical Devices Regulation
12. Protection of Pregnant and Breastfeeding Workers Directive
13. Safety and Health of Workers at Work Directive
14. Safety and/or Health Signs at Work Directive
15. Waste Framework Directive

In addition, as indicated in ECHA disseminated database, installations using 1,3-diphenylguanidine may be subjected (due to its classification Hazardous to the Aquatic Environment in Category Chronic 2) to industrial accident prevention and reporting requirements in accordance to the Seveso III Directive (Directive 2012/18/EU)[[3]](#footnote-4).

According to Gestis substance database[[4]](#footnote-5), no occupational exposure limits (OELs) values exist at the European level for this substance. Biological limit values (BLVs) or biological guidance values (BGVs) are not recommended by the scientific committee on occupational exposure limits (SCOEL, 2014).

## Information on tonnage and uses

Table 3: Tonnage and registration status

|  |  |
| --- | --- |
| From ECHA dissemination site[[5]](#footnote-6) | |
| Registrations | Full registration(s)  (Art. 10)  Intermediate registration(s)  (Art. 17 and/or 18) |
| Total tonnage band for substance (excluding volume registered under Art 17 or Art 18, or directly exported) | 10,000-100,000 tpa |

The registered tonnage of the substance has increased from 1,000-10,000 tpa during substance evaluation to 10,000-100,000 tpa nowadays.

DPG is mainly used in the manufacture of rubber as a vulcanizing agent and vulcanizing accelerator. This substance is used in the manufacture of general rubber goods and tyres. As indicated by the Registrants, the substance can be found in articles like pipes and tubes, rubber shoes, mattresses, conveyor belts, hygiene items or inflatable toys. Literature also reported the presence of DPG in articles such as medical gloves (Hamnerius *et al*. 2014, Crepy 2016). A detailed overview of uses and related exposure scenario for human health and the environment is available in Annex I.

## Hazard information (including classification)

A comprehensive hazard assessment was performed and is available in the SEv conclusion document (ANSES, 2020)[[6]](#footnote-7).

### Classification

1,3-diphenylguanidine (DPG) has an harmonised classification under CLP regulation.

**Table 4: Harmonised classification according to Annex VI of CLP regulation (Regulation (EC) 1272/2008)**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Index No** | **International Chemical Identification** | **EC No** | **CAS No** | **Classification** | | **Specific Conc. Limits, M-factors** | **Notes** |
| **Hazard Class and Category Code(s)** | **Hazard statement Code(s)** |
| 612-149-00-4 | 1,3-diphenylguanidine | 203-002-1 | 102-06-7 | Repr. 2  Acute Tox. 4 \*  Eye Irrit. 2  STOT SE 3  Skin Irrit. 2  Aquatic Chronic 2 | H361f \*\*\*  H302  H319  H335  H315  H411 | - | - |

In addition, the following hazard classes are notified among the aggregated self-classifications in the C&L Inventory:

Acute Tox. 3 - H301

Acute Tox. 4 - H302

Skin Irrit. 2 - H315

Eye Irrit. 2 - H319

Eye Dam. 1 - H318

STOT SE 3 - H335

Repr. 1B – H360FD

Repr. 2 - H361f

Aquatic Chronic 2 - H411

Aquatic Chronic 3 - H412

**Table 5: CLP Notifications**

|  |  |
| --- | --- |
|  | **CLP Notifications**[[7]](#footnote-8) |
| Number of aggregated notifications | 20 |
| Total number of notifiers | 558 |

Following the conclusion mentioned in the SEv conclusion report, an update of the harmonized classification is considered justified.

It is proposed to add classification for Skin Sens. 1 (H317) and to modify Acute Tox. 4 (H302) to Acute Tox. 3 (H301), Eye irrit. 2 (H315) to Eye Dam. 1 (H318) and Aquatic Chronic 2 (H411) to Aquatic Chronic 3 (H412).

Uncertainties in the mutagenic potential of DPG due to positive results in stomach and clear species differences in mutagenic potential were noticed. Nevertheless, although positive Ames assays were observed with hamster S9 mix, negative results using both rat and human S9 mix are reassuring. In conclusion, based on the available database and weight-of-evidence, no mutagenicity classification is warranted for DPG.

In addition to the endpoints identified during SEv, the analysis of the recent EOGRTS warrant a classification Repr. 1B for fertility and development. In addition, regarding neurotoxicity, a classification STOT RE 2 (nervous system) is also considered justified for the substance.

The update of the harmonised classification is ongoing and the following modifications will be proposed by the aMSCA.

**Table 6: Proposed harmonised classification and labelling according to the CLP criteria**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **International Chemical Identification** | **Classification** | | **Labelling** | | **Specific Conc. Limits, M-factors** |
| **Hazard Class and Category Code(s)** | **Hazard statement Code(s)** | **Pictogram, Signal Word Code(s)** | **Hazard statement Code(s)** |
| Current Annex VI entry | 1,3-diphenylguanidine EC No 203-002-1 CAS No 102-06-7 | Repr. 2  Acute Tox. 4 \*  Eye Irrit. 2  STOT SE 3  Skin Irrit. 2  Aquatic Chronic 2 | H361f \*\*\*  H302  H319  H335  H315  H411 | GHS08  GHS07  GHS09  Wng | H361f \*\*\*  H302  H319  H335  H315  H411 |  |
| Dossier submitters proposal | 1,3-diphenylguanidine EC No 203-002-1 CAS No 102-06-7 | Repr. 1B  Acute Tox. 3  Eye Dam. 1  Skin Irrit. 2  Skin Sens. 1  STOT RE.2  STOT SE 3  Aquatic chronic 3 | H360 FD  H301  H318  H315  H317  H373  H335  H412 | GHS 08  GHS 06  GHS 05  GHS 07  Dgr | H360 FD  H301  H318  H315  H317  H373  H335  H412 | Oral: ATE=110 mg/kg |

### Setting of DNELs considering the recent EOGRTS study

The EOGRTS study is a key study for reproductive toxicity and the effects observed were considered relevant for DNEL derivation. Indeed, significant pups mortality was observed in F1 lactating pups from 5 mg/kg bw/d during PND1 to 4. The same tendency was recorded in F2 lactating pups with statistical significance at the mid dose. Considering the severity of this effect and its statistically significance at the lowest dose in F1, it was considered as the critical effect, and the LOAEL of 5 mg/kg bw/d as Point of Departure (PoD) for the calculation of the Derived no effect level (DNEL) for reproductive toxicity of DPG. Assessment factors were applied in accordance to ECHA guidance document R8(ECHA, 2012).

When the starting point for the DNEL calculation is a LOAEL, an assessment factor (dose-response assessment factor) ranging from 3 (as minimum/majority of cases) to 10 (as maximum/exceptional cases) is applied. Considering the severity of the effect (mortality of pups) and the uncertainties regarding the shape and slope of the dose-response curve, an increase of the assessment factor is justified. Considering also that the effect is characterized from a study of good quality and of relevant statistical power, the aMSCA recommends an assessment factor of 5 for the extrapolation of the LOAEL to the NOAEL.

The DNELs as calculated by the aMSCA are listed in the table below.

**Table 7: DNEL revision according to the aMSCA**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Endpoint of concern | Type of effects | Population | Route of exposure | dose descriptor | Corrected starting point | Total assessment factor | DNELs |
| Reproductive toxicity | Post-natal mortality of pups | Workers | Inhalation | LOAEL = 5 mg/kg bw/d | 12.3 mg/m3 | 62.5 | 0.197 mg/m3 |
| Dermal | 70 mg/kg bw/d | 250 | 0.280 mg/kg bw/d |
| Consumers | Oral | 5 mg/kg bw/d | 500 | 0.010 mg/kg bw/d |
| Inhalation | 4.35 mg/m3 | 125 | 0.035 mg/m3 |
| Dermal | 50 mg/kg bw/d | 500 | 0.100 mg/kg bw/d |

The detailed revision of the DNEL on the basis of this study is available in Annex I (section 2.1.1).

The DNELs recommended by the aMSCA are below Registrants’ DNEL due to the use of an assessment factor of 5 instead of 3 for dose-reponse/severity.

### Endocrine disruption properties assessment

In 2020, ANSES published the substance evaluation conclusion report on DPG (ANSES, 2020). No conclusion on endocrine disrupting properties could have been made at that time as a datagap covering adverse effects on the full range of reproductive endpoints was identified. It was recommended to reassess the DPG for potential endocrine disruptor properties following the analysis of the requested EOGRTS study.

After reception of the EOGRTS study on rats (unpublished study report, 2021), several reproductive and developmental effects raised concerns about endocrine disruption properties of DPG:

- Increase in adrenal gland weight

- Effects on thyroid hormones

- Two females developed an adenocarcinoma in mammary gland

- An increased duration of gestation was observed on an individual basis

- Females presenting reproduction difficulties

- Post-implantation loss

- Estrous cycle alterations

Changes in estrous cyclicity was also observed in rats and mice in a NTP 90-day study (NTP, 1995).

DPG underwent testing for endocrine disruption potential using the Tier 1 screening assays developed for the U.S. EPA’s EDSP (Kreider & Panko, 2016). The published information indicates, on the basis of the weight of evidence (WoE) analysis, that DPG is unlikely to act as an endocrine disruptor through EATS modes of action. This information was complemented with a literature review of the potential mode of action of DPG, ToxCast data, Danish QSAR data and OECD QSAR Toolbox data on DPG. Additional OECD level 1 and 2 data did not bring relevant information pointing toward an endocrine activity.

Although reprotoxic adverse effects were noted for the substance DPG, it is not possible on the basis of the available data to establish an endocrine mode of action corresponding to the adverse effects.

Thus, there are no sufficient indications to consider that the substance has ED properties. A detailed assessment of the information available can be found in Annex I (section 2.1.2). A summary of the EOGRTS study is available in Annex I (section 2.1.3).

### Hazards related to degradation products and impurities

As mentioned in the registration dossier, the major degradation products of DPG consist of aniline (CAS no. 62-53-3, EC no. 200-539-3), N-nitroso-diphenylurea and phenyl guanidine. In addition, aniline is also present as an impurity (ANSES, 2020). Aniline is the only chemical among these degradation products which is registered under REACh regulation. This substance has a harmonised classification (index number 612-008-00-7)[[8]](#footnote-9) under CLP regulation. The hazard class and categories of aniline include acute toxicity 3, eye damage 1, skin sensitive 1, mutagenic 2, carcinogenic 2, repeated toxicity 1 and aquatic acute toxicity 1. On the basis of its classification as carcinogenic category 2 and mutagenic category 2, Aniline was included in the Commission Directive (EU) 2021/903[[9]](#footnote-10) which is an amendment to EU Toy Safety Directive (TSD) Directive 2009/48/EC (EU TSD) on 4 June 2021. Specific limit values for aniline were established for certain categories of toys. Worst-case concentration of aniline in articles (≤0.0041%) was provided by the Registrants and a risk assessment for all uses mentioned in the CSR was performed during the substance evaluation process. With regard to aniline risk assessment, RCR < 1 were calculated and no further risk management is needed. No new data were added to the dossier and aniline was not reassessed in the course of this RMOA.

It was not possible to evaluate the hazards and risk related to the two other degradation products. No toxicological profile or data on the concentration of these substances in products containing DPG or in derivatives rubber articles is available. No information has been identified in the literature that investigates the presence of DPG degradation products N-nitroso-diphenylurea and phenyl guanidine in rubber articles. An alkylating potential of nitrosophenylurea (a mono-alkylated analogous substance) is identified although its potency is 20,000-fold lower than for others N-alkyl-N-nitrosourea, nitrosomethylurea for example (Manso et *al*. 2008). The carcinogenic action of nitrosophenylurea was also investigated in a non-guideline study by Lijinski & Winter (1981), and was found to induce skin tumors in 1 out of 20 mice. In comparison, nitrosomethylurea was found to induce tumors in 11 out of 20 mice. By analogy, N-nitroso-diphenylurea is expected to induce similar effects to the mono-alkylated analogous substance nitrosophenylurea. Thus, no clear conclusion on carcinogenic potential can be drawn. Due to the absence of reliable information on hazard and exposure of N-nitroso-diphenylurea and phenyl guanidine, further investigations could not proceed.

In addition, 1,3-diphenylurea was pointed out in the literature as a degradation product of 1,3-diphenylguanidine. This substance, with a low potential for toxicity (self-classification Acute Tox. 4), was not reported as a degradation product by the Registrants.

## Exposure and risk characterisation

The aMSCA noticed that, since the publication of the conclusion document in 2020, the quantity of DPG manufactured in and / or imported to the European Economic Area increased from ≥ 1000 to < 10,000 tonnes/year to ≥ 10,000 to < 100,000 tonnes/year.

### Exposure and risk characterisation for Human Health

In the context of this RMOA, only the latest version of the CSR that have been revised further to the recent EOGRTS (2021) study were analysed.

Overall, 24 exposure scenarios were considered. The scenarios are related to: manufacturing of DPG, formulation and re-packaging, manufacturing of General rubber goods and tyres, use of tyres, storage of used tyres before recycling, tyres recycling (End of Life Tyres, ELT), re-use of ELT and use of General Rubber Goods (GRG) articles.

The exposure assessment was based on the chemical safety report as provided by the Registrants. CHESAR 3.6 with in-built ECETOC TRA was used by Registrants for Tier 1 modelisation and RISKOF DERM and ART for Tier 2 for workers. For consumers, the tools used by Registrants were ECETOC TRA for tier 1 and/or ConsExpo for Tier 2.

The Risk characterisation ratio (RCRs) were calculated for workers and general population considering the updated long-term DNEL based on reproductive toxicity. As detailed in the section 1.4.2, the DNELs were reassessed by aMSCA. The DNELs recommended by aMSCA are below Registrants’ DNEL due to the use of an assessment factor of 5 instead of 3 for dose-response/severity.

The exposure scenarios, the associated PROCs and the calculated risks are detailed in tables 21 and 26 in annex I.

Overall, RCR > 1 are observed in contributing scenario of most exposure scenarios for industrial and professional workers and in one scenario for consumers.

For industrial workers, contributing scenario leading to RCR > 1 were identified in several exposure scenarios. The RCRs calculated were between >1 and 1.61.

Considering professional workers, contributing scenario with RCR > 1 were identified for:

1. exposure scenario 6 (Service life (professional worker) - GRG articles - conveyor belt),
2. exposure scenario 12 (Service life (professional worker) - End of Life Tyre: ELT pre-processing storage.),
3. exposure scenario 21 (Service life (professional worker) - ELT articles – installation of shock absorbing tiles)
4. exposure scenario 23 (Service life (professional worker) – re-use of ELT articles – installation of synthetic turf fields).

The RCRs calculated were between > 1 and 1.31.

For consumers, the contributing scenario 2 of the exposure scenario 11 (Service life (consumers) - Consumer use of tyres (vehicles)) present a RCR for dermal route equal to 1.12 and a RCR for combined routes equal to 1.13. The situation considered for RCR calculation was a worst case situation of new tyre change (higher % of DPG compare to used tyre) with a % of DPG value of 0.08 (% of DPG in full new tyre). DPG content in used tyres is considered to be 0.04%. In this scenario, only the Tier I tool ECETOC TRA has been used. On the other hand, no data have been identified by the aMSCA to confirm the concentration of DPG present in tyres, whether manufactured in Europe or imported from outside Europe.

**Exposure to DPG reported in literature and potential risks**

**Presence of DPG in gloves and shoes**

Contact allergy to DPG is largely reported in the literature (Hansen *et al*. 2021). The main type of reactions and population identified are sensitization reactions to rubber gloves in healthcare workers. Indeed, the presence of DPG is reported in rubber gloves (Dejonckheere *et al*. 2019, Hamnerius *et al*. 2014, Crepy 2016). These studies were conducted in different countries worldwide. Several other studies report foot dermatitis due to the presence of DPG in shoes (Traidl *et al*. 2021, Suhail *et al*. 2009, Saha *et al*. 1993, Ross 1969).

Corazza *et al*. (2021) also reported the presence of DPG in boxing gloves.

A harmonized classification as Skin Sens. 1A, H317 is proposed by aMSCA.

**Presence of DPG in drinking water**

Several recent publications indicate the presence of DPG in drinking water sources, drinking water treatment plants and drinking water.

Zhang *et al*. (2023) studied the presence of tire additives in drinking water treatment plant. The presence of DPG and 1,3-diphenylurea, a transformation product of DPG, were reported. In the source samples of drinking water, the authors indicated that the concentration of detected accelerators (which included DPG and 1,3-diphenylurea) ranged from 35.5 ng/L to 183 ng/L. In the DWTP samples, concentrations of detected compounds (which included DPG and 1,3-diphenylurea) ranged from tens to hundreds of nanograms per liter.

Ichihara *et al*. (2023) analyzed the presence of guanidine derivatives in different type of water in Japan. DPG was detected in tap water with frequency of detection of 100% from 2 samples (concentration not specified).

Gollong *et al*. (2022), analyzed the presence of chemicals in a drinking water production and wastewater treatment plant in Germany. DPG was detected at a median concentration of 4 ng/L (probably a median of the concentration of DPG in all types of water tested in the study, not only drinking water).

One of the possible source of DPG emission may be the migration from water pipe designed to transport treated drinking water. Tang *et al*. (2015) investigated the presence and distribution of selected semi-volatile organic compounds from source water to tap water in Changsha, China. The potential migration of specific compounds from pipe material into water at different periods of pipeline life was studied. DPG was found to be migrating from high density polyethylene (HDPE) pipe material. DPG was found in drinking water at different sampling sites at concentrations up to 0.56 mg/L (0.23-0.47 mg/L in the residential district).

Diera *et al*. (2023) studied the migration of compounds from high-density polyethylene pipes in a drinking water distribution system in Denmark. Among them DPG was detected in the water. The proposed origin was polyethylene (PE) and rubber seals. Five rubber seals from different valves commonly used in the water distribution system, consisting of EPDM (Ethylene Propylene Diene Monomer Rubber) and NBR (Nitrile Butadiene Rubber) rubber were investigated. DPG was found in EPDM rubber gasket plate, which is used to make custom gaskets in waterworks. DPG is included in the positive list (Combined List – lists of substances under review) of the 4MSI Common Approach on Organic Materials in Contact with Drinking Water[[10]](#footnote-11). The NL authority member state indicate a Maximum Tolerable Concentration (MTC) of 0.0025 mg/L for the use of this substance as rubber in contact with drinking water.

DPG was also detected in drinking water sources in Germany (Neuwald *et al*. 2022) at a median concentration of 0.17 ng/L with a frequency of detection of 17%. The authors also studied the emission pattern of 34 substances by using a correlation analysis to investigate patterns of co-occurrence. DPG did not correlate well with the other compounds tested and the authors concluded that DPG emission into drinking water sources is likely related to leachate from road run-off during rain events and that consequently DPG concentrations may be more dependent on the sampling time than on the sampling location.

**Presence of DPG in indoor dust**

The presence of DPG was reported in indoor dust.

Tan *et al*. (2021) studied the presence of synthetic antioxidants in house dust from different locations in the Asia-Pacific Region and the United States. Among them, DPG was detected with a median concentration of 5030−11 400 ng/g in house dust from the studied regions except for Hanoi (305 ng/g).

Li & Kannan (2023) studied the occurrence of DPG in indoor dust from 11 countries. DPG was found in 100% of the house dust samples, at median concentrations of 140 ng/g (range: 2.1 – 11 000 ng/g). Elevated concentrations of DPG were found in dust from certain microenvironments (e.g., offices and cars). The authors assessed human exposure to DPG through dust ingestion and the following ranges were 0.07−4.40, 0.09−5.20, 0.03−1.70, 0.02−1.04, and 0.01−0.87 ng/kg bw/day for infants, toddlers, children, teenagers, and adults, respectively.

Shin *et al*. (2020) measured the concentrations of consumer product chemicals in California house dust. The median concentration of DPG was 3218 ng/g of dust and was detected in all dust samples.

**Presence of DPG in air**

Johannessen *et al*. (2022) studied the airborne concentrations of chemicals associated with tire-wear in megacities using passive samplers. DPG was detected in every studied megacity above limits of quantification at estimated concentrations between 45.0 to 199 pg/m3 (mean = 93.9 pg/m3). DPG was detected in the highest estimated concentration out of any analyte included in this study.

**Other contamination with DPG**

Lin *et al*. (2007) detected a contaminant during the content uniformity test of a drug product (tablet formulation) and concluded that it was most likely DPG. They proposed as the potential source of DPG as coming from the safety filler of the pipette bulb used to prepare the sample solutions during the drug analysis.

Zidan *et al*. (2017) also detected the presence of DPG in a pharmaceutical product (oxytocin). DPG was coming from rubber closures used in pre-filled syringes. DPG was able to interact with oxytocin.

**Risk estimations based on literature data**

It is highlighted that data are scarce and have limitations. These calculations are therefore performed to obtain an estimates whether risks may occur through the different reported sources of exposures.

**Drinking water:**

Risk calculation was performed based on publications where a specific concentration of DPG was clearly indicated.

In Gollong *et al*. (2022), the concentration indicated is probably a median of DPG concentrations in all the types of water tested in the study and therefore not specific to drinking water samples.

In Neuwald *et al*. (2022), the concentration of DPG was calculated in sources of drinking water and not in the treated water.

In Tang *et al*. (2015), the maximum DPG concentration in the residential district has been selected (0.47 mg/L) for risk estimation.

The exposure assessment is based on the following calculation method (Anses, 2018):

Exposure = Cwater x consumption/ bw

Where:

**Exposure:** µg/kg bw/d

**Cwater:** concentration of DPG in water in µg/L

**Consumption:** 2L/d for adults, 1L/d for children, 0.75 L/d for infants (WHO, 2022)

**bw:** 60 kg for adults, 10 kg for children, 5 kg for infants (WHO, 2022)

Table 8: Exposure and risk characterisation in drinking water

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Publications | Concentrations of DPG (µg/L) | Concentration type | Exposure (µg/kg bw/d) | | DNELoral (µg/kg bw/d) | Risk characterization | |
| Gollong *et al*. 2022 | 4.10-3 | Median concentration | Adults | 1.33.10-4 | 10 | Adults | 1.33.10-5 |
| Children | 4.10-4 | Children | 4.10-5 |
| Infants | 6.10-4 | Infants | 6.10-5 |
| Tang *et al*. 2015 | 470 | Maximal concentration | Adults | 15.67 | Adults | 1.567 |
| Children | 47 | Children | 4.7 |
| Infants | 70.5 | Infants | 7.05 |
| Neuwald *et al*. 2022 | 1.7.10-4 | Median concentration | Adults | 5.67.10-6 | Adults | 5.67.10-7 |
| Children | 1.7.10-5 | Children | 1.7.10-6 |
| Infants | 2.55.10-5 | Infants | 2.55.10-6 |

Overall, risks were highlighted when the maximal DPG concentration from the Tang *et al*. (2015) study was considered. In this study, DPG is found to be migrating from high density polyethylene (HDPE) pipe material used for water distribution. It is important to note that there are significant disparities in DPG concentrations between the publications that could be related to the source and quality of water, and the value used to describe the data set (maximal or median concentration).

**Dust ingestion:**

Risk estimation was performed for the publication below in where an exposure assessment to DPG was conducted.

Li & Kannan (2023) assessed human exposure to DPG through dust ingestion and the following ranges were 0.07−4.40, 0.09−5.20, 0.03−1.70, 0.02−1.04, and 0.01−0.87 ng/kg body weight (BW)/day for infants, toddlers, children, teenagers, and adults, respectively. These exposure are all below the DNEL recommended by aMSCA. Concentrations reported in other studies (Tan *et al*., 2021 and Shin *et al*., 2020) were in the same range of concentrations.

**In conclusion, when considering all the exposure scenarios presented in the CSRs and the revised DNELs recommended by the aMSCA, some RCR are between >1 and 1.61:**

1. **most scenarios for industrial workers and several scenarios for professional workers**
2. **change of new tyres by consumers (RCR =1.13)**

It has to be noted that in most of the exposure scenario (except for scenario 1a and 1b), only a Tier I assessment tool was used. Moreover, dermal route is identified as a significant route of exposure in many of the exposure scenario in which RCR were greater than 1 and the RMMs did not systematically include glove wearing. Gloves may be added to lower the risks. Additional operational conditions (OCs) and RMMs may be also implemented. However, it is noted that implementation and compliance to additional OCs and RMMs may be more difficult to achieve in professional situations than in industrial installation.

**Considering the low magnitude of risks, exposure assessment with Tier II tools and addition of RMM may result in refinement and possibly control of risks. The aMSCA therefore recommend that registration dossiers above 10 tpa are updated considering the DNEL as described in section 1.4.2 and section 2.1.1 of Annex I to provide demonstration that risks are adequately controlled for all registered uses of the substance.** It is however not possible for the aMSCA to go further in the analysis. Despite a refinement and the addition of OCs and RMMs, there is a possibility that risks remain.

**Besides, in addition to the information given in the CSR, data from the literature provided indications of sources of exposure to DPG.** Contact allergy due to the presence of DPG in gloves, shoes and socks is reported. DPG was detected in drinking water and drinking water sources in several publications. DPG was also detected in indoor dust and in the air of megacities in countries across the word. It can be noted that DPG concentrations varied a lot between publications. This may be explained by the differences of sensitivity in the detection methods. Other parameters may also have influenced but are not known. The identified and possible sources include releases from tire particles, from the use of rubber goods and in particular from pipes used in drinking water distribution. One publication also reported the contamination of pharmaceutical products by DPG coming from the material used to manipulate the drugs.

Risk calculation were performed with the concentrations of DPG in water (drinking water and drinking water sources) from 3 publications. Risks were determined for infants, children and adults for the concentration of 470 µg/L of DPG in drinking water (Tang et al. 2015). The origin of DPG in this publication is from migration from HDPE pipes material. This type of pipe is also used in Europe (Diera *et al*., 2023). However, it is difficult to know if the material composition in China and in Europe is similar. Therefore, it is not known whether the concentration reported in the publication of Tang *et al*. (2015) is representative of the DPG concentration in drinking water in Europe. Nevertheless, a potential risk due to the presence of DPG in drinking water cannot be dismissed.

Overall, DPG has been detected in many sources other than those covered by the exposure scenario of the CSRs and the extent of the articles where DPG is present is not known. **This raise uncertainties on the representativeness of the exposure scenarios presented in the CSR regarding the possible extent of the articles in which DPG is present. There are also uncertainties on the residual amount of DPG present in articles for which no data has been found in the literature.**

The exposure of DPG to the general population is therefore from multiple sources and appears to be continuous. As a classification as Repr. 1B – H360FD is proposed by aMSCA, the presence of DPG in many sources raise concern.

### Exposure and risk characterisation for the environment

Based on the aMSCA assessment of exposure scenarios available in the registration dossiers, environmental risk assessment shows unacceptable risks for exposure to surface water and sediment in scenario 1a (Manufacture of the substance-Registrant 1) following direct release of the substance to the water. This conclusion differ from the registrant. The aMSCA revised the flow rate of the river and the dilution factor which were found to be inaccurate. This corrected value has a major impact on the dilution of DPG in the water course and the overall risk calculation.

Environmental risk assessment shows unacceptable risks for exposure to agricultural soil and groundwater in scenario 1b (Manufacture of the substance-Registrant 2) following effluent treatment in the sewage treatment plant located on the site of the manufacture. However, the registrant mentioned that no application of the STP sludge is made on agricultural soil and that particular considerations are made on the waste treatment operations. Thus, the aMSCA considers that the risks are acceptable if the appropriate risk management measure are applied.

Environmental risk assessment shows unacceptable risk for scenarios 2, 3 and 4 (Formulation or re-packing scenarios) for fresh water and sediments following direct release of the substance to the water. In these scenarios, the Registrants mentioned that there is no DPG-containing wastewater in this process. The aMSCA considers the zero emission as an unrealistic emission scenario and applied the default value for release to wastewater as indicated in the R.16 Guidance document. A "zero release" from installations is usually not applicable. In occupational exposure assessment, the "no or zero exposure" when substances are used by workers is not accepted. If the substance is used in closed systems, there is always exposure (at least due to unavoidable leakages) though possibly on a very low level. In addition, it is highly likely that the powdered substance will be released to and distributed in the environment. At least during the cleaning of the facility, the use of water is highly likely.

However, from a regulatory perspective, "no release" on local level can be assumed in case the substance is handled under operational conditions that are comparable to "strictly controlled conditions" for isolated intermediates. Moreover, additional information was provided by one of the two manufacturers for scenario 2 (F - Formulation or re-packing – Masterbatches manufacture). In the confidential document submitted (personal communication to the aMSCA), the registrant gives details on the processes of formulation, the operators’ duties, and the cleaning and waste management. It is mentioned that the bags use for packaging, the floor and equipment are not washed with water. The waste (bags) is monitored. The mixing tank cleaning is done dry or scraping with rags soaked in solvent, there is no cleaning with water installation. The extruder is cooled with cold water but the cooling system is tight and not in contact with the product. Information on frequency and the recommended cleaning technique, and what happens with the solid waste and waste water from wet cleaning is crucial. These measures, if applied correctly, allow to reduce efficiently the release of DPG in the environment. Thus, the aMSCA considers the risks acceptable following the application of appropriate risk management measure as indicated by the registrant.

**After consideration of the risks identified for the surface water and sediment at the industrial sites, and in the absence of data from the Registrants mentioning the concentration of the substance in the water course, the aMSCA is of the opinion that measurements and monitoring data (samples to be taken at relevant release events) in surface water are necessary to confirm that the appropriate risk management measure are effective in limiting the emission of DPG in the environment to a safe level. A** **more detailed description of the operational conditions should be provided for the second manufacturer as well.**

Scenario 8 and 9 (Manufacture of Tyres) indicated that the predicted environmental concentration of DPG is 0.15 µg/L in groundwater. Monitoring data obtained from Norman database[[11]](#footnote-12) and the literature review (as detailed in Annex I section 3.2.5) also indicated the presence of DPG in the aquatic environment. There is however an uncertainty whether the available surface water monitoring data represent local assessment (as closely as possible to the emission source) that inform in particular on industrial uses for which risks are identified. The source could come from industrial releases of DPG in water. However, the occurrence and widespread distribution of DPG in the aquatic environment indicate a diffuse form of pollution.

From the Norman database, the reported values are lower than the PNEC for surface water (30 µg/L). However, the samples might not be fully representative of the environmental situation as they were obtained in only one campaign of 3 months in 2019, and they come from a single hydro-geological region of Eastern Europe (Danube river basin).

The monitoring values from the literature, at the exception of surface runoff following intermittent rainfall events, are also under the hazard threshold values (PNEC values) for the aquatic environment. This indicate the absence of risk for aquatic organisms following the uses of DPG, at the exception of particular or punctual events. In addition, the increase in the concentration of DPG in the aquatic environment after a rainfall event could allow to link the widespread occurrence of DPG to other sources of pollution. Exposure scenarios as developed by the registrants are limited to the manufacture and formulation of DPG, and consider a limited amount of manufactured articles. Uncertainties remain regarding additional exposure scenarios that might cover the diversity of articles containing DPG, give information on the concentration of DPG in articles or take into account the release of DPG during the service life of articles (leaching). The exposure and risks related to tyres abrasion and release of DPG in the aquatic environment is of concern. Monitoring information showed that DPG is a ubiquitous substance and literature indicate that tyres abrasion could be a major source of DPG release in the environment. However, the exposure scenarios as provided in the registration dossier do not reflect the exposition of the substance to the aquatic environment as found in the literature and do not consider the risk associated to tyres abrasion or leaching from other rubber articles.

Also, the mobility property of DPG needs to be considered as it might not be efficiently removed from the WWTP (including domestic or municipal sewage treatment plants-STP or industrial wastewater treatment plants). Monitoring the influent and effluent concentration of DPG at the WWTP could help understand the behaviour and fate of the substance. The higher concentration of DPG found in monitoring data from WWTP compared to the other aquatic environment raised the question if the exposure scenarios proposed by the Registrants cover all the uses of DPG. In particular, the release of DPG from high density polyethylene (HDPE) pipe material use for drinking water distribution is of concern.

Due to the possibility that rubber is used in a very wide range of articles, the aMSCA identifies uncertainties on whether all sources of exposure to humans and the environment from articles are identified and assessed in the registration dossier.

## Information on vulcanization by-products and alternatives

The problems caused by the formation of nitrosamines during the vulcanization of rubbers have long been known. Thirteen nitrosamines are classified Carc. 1B by CLP (Ineris, 2014) and cancer mortality has been associated with exposure to nitrosamines in rubber workers (Straif, 2000), so that their formation or presence must be prevented. The major source of nitrosamines in rubber products is amine-containing accelerators. This question was therefore further investigated in relation to DPG.

Nitrosamines and nitrosatable substances formation requires both a substrate of the nitrosatable substrate type (primary amine, secondary amine or quaternary ammonium salt) and a nitrosating agent (for example nitrates) (ANSES, 2012). Nitrosamines are brought into rubber products during vulcanization steps as a result of the nitrosation of secondary aminated vulcanization accelerators with nitrogen oxides in the industrial atmosphere and/or nitrites of uncertain origin. Nitrosamines migrate to the surface of rubber products during storage and usage.

Data are available to assess the presence and the risk related to the presence of nitrosamine in consumers products and articles. Migration of nitrosamines from various latex products; e.g., nipples, condoms, gloves and balloons has been studied as reported in Feng *et al*. (2012). The authors found that, of 20 sampled gloves and balloons, 85% released nitrosamines above the recommended limit in Directive 93/11/EEC. This European directive 93/11/CEE concerning the release of the N-nitrosamines and N-nitrosatable substances from elastomer or rubber teats and soothers prohibit the trade in and use of articles which do not comply with a limit of 0,01 mg in total of N-nitrosamines released/kg and 0,1 mg in total of N-nitrosatable substances/kg. Also, the European directive 2009/48/CE prohibited the use of nitrosamines and nitrosatable substances in toys intended for use by children under 36 months or in other toys intended to be placed in the mouth if the migration of the substances is equal to or higher than 0.05 mg/kg for nitrosamines and 1 mg/kg for nitrosatable substances.

Focusing on nitrosamines emissions from rubber infill, RIVM surveyed in 2007 an experimental assay in order to characterise nitrosamines emissions above football pitches. None of the air samples nor the materials analysis showed the presence of nitrosamines (all below the detection limit). They were only released in two migration tests at a limited extent (4.5 µg/kg). RIVM concluded nitrosamines did not pose a health issue from synthetic turf fields (RIVM, 2007, cited in ANSES 2018).

According to the Ineris document (2014), the reduction of nitrosamine formation could be achieve if one, or many, of the following techniques are used:

- Nitrosation inhibitor addition (alpha-tocophérol, urea, acide amidosulfonique);

- Elimination of nitrosing agent (nitrite-free formulated salt);

- Elimination of secondary amines sources responsible of generating nitrosamines (by substitution or the use of a different technique);

- Use of another mode of vulcanization (replacing the chemical process using nitrate and nitrite by an heating process using hot air oven or microwaves),

Substitution of accelerators forming harmful nitrosamines is already ongoing. Patent describing a rubber composition free of carcinogenic nitrosamine precursors have been published and DPG is mentioned as an alternative to carcinogenic nitrosamine precursors (European Patent office EP0695780B2, 2006). This alternative however does not prevent totally the presence of nitrosamines in articles.

Moreover, the Registrants present DPG as a nitrosamine-free accelerator for vulcanization of rubbers. This statement is also in line with the Ineris (2014) document mentioning that DPG is one of the substitute substances (together with ZBEC (Zinc dibenzyl Dithiocarbamate), CBS (N-Cyclohexyl-2-benzothiazole sulfenamide), TBzTD (Tetrabenzylthiuram Disulfide) and MBT (2-mercapto Benzothiazole)) which can suppress the sources of secondary amines leading to nitrosamines formation. Finally, the degradation products aniline, N-nitrosodiphenylurea and phenyl guanidine are not identified as nitrosamines and are not listed as classified nitrosamines in the Ineris document. Nitrosodiphenylurea is rather identified as nitrosourea for which scarce data are available.

New techniques are also evolving, for example using the inclusion complex of diphenylguanidine-hydroxypropyl-β-cyclodextrin (DPG-HP-β-CD) by ball milling has been shown to improve the water solubility, bioavailability, reliable stability, and low toxicity (Zhang *et al*., 2022). As indicated by the authors, this technique could help reduce the usage of DPG, leading to the reduction of toxicity and environmental hazards.

**For public consultation:**

Additional information are welcome regarding the presence and risks related to degradation products of DPG, by-products formation in the manufacture and formulation steps involving DPG, and the substances and processes involved in the vulcanization of rubbers used for general rubber goods and tyres production.

# Justification for the need for regulatory risk management action at EU level

## Need for (further) risk management

In the course of this RMOA process, the aMSCA identified relevant human health hazards of DPG that may triggers further management measures in relation to consumers and workers exposure. These hazards relate to toxicity for the reproduction, repeated toxicity (inducing neurotoxicity) and skin sensitisation. Risk characterization of the substance also indicated that risk for environment, consumers and workers for the use of DPG are not fully covered. DPG is manufactured and imported to the EU in amounts of 10,000-100,000 tpa and is found in a variety of articles in the EU market as general rubber goods, tyres or usage of granulates from end-of-life tyres (ELT) reconverted into shock absorbing titles in playgrounds or in synthetic turf field. Its widespread presence and related hazards and risks when considering a revised DNEL justify the consideration of further risk management measure.

Occupational safety and health of workers

DPG displays hazardous properties for human health and a revision of the harmonized classification to include Repro 1B, H360fd, Skin Sens. 1 H317, and STOT RE 2, H373, is ongoing. DPG is a high tonnage substance produced in the EU which raises concern for the safety of workers at industrial sites as well as for the professional worker.

Using the available toxicological data and a conservative approach, the aMSCA derived dermal and inhalation DNELs for workers. These values are lower compared to the Registrants values and the aMSCA identified exposure scenarios where the safe use is no longer demonstrated (RCRs up to 1.61).

Environment and indirect exposure of the general population

Risk characterisation from exposure scenarios of DPG as presented by the Registrants and evaluated by the aMSCA can be prevented by adequate mitigation measures, if applied correctly. However, a release of DPG into the aquatic environment from production sites, and general rubber goods and tyres cannot be excluded at the moment. In particular, the exposure scenario as submitted by the registrants did not considered leaching of DPG from articles during their service life. DPG is present in Europe’s aquatic environment as indicated in the scientific literature and monitoring database such as NORMANN. Emissions are likely to result from the manufacture and use of the substance in general rubber goods articles and tyres. DPG has been shown to leach from tyre wear materials. Tyre wear particles enter road surface with the friction between tyres and road surfaces. Under the volatilization, leaching, and transformation action by sunlight and rain, tyre additives are released into urban water systems, such as surface rainfall runoff, sewage treatment plants (STPs), receiving surface waters, and drinking water treatment plant (DWTP).

Given its mobility in the aquatic environment and its toxicological profile, DPG triggered the hazard to the quality of water resources. DPG might not be efficiently removed from the WWTP (including domestic or municipal sewage treatment plants-STP or industrial wastewater treatment plants) due to its mobility property and the short time of residency in the water treatment plant. Release of DPG from pipes and tubes has been demonstrated and its presence in drinking water is insufficiently monitored. Uncertainties remain regarding additional articles that could be sources of release of DPG to the environment. Adequate measures must be put into place to ensure and preserve water safety and quality.

Consumer exposure

Consumers are exposed to a wide variety of rubber articles. The aMSCA revised the oral, dermal and inhalation DNELs for consumers and has identified risk related to the exposure of consumer use of tyres (vehicles). Uncertainties remain regarding the representativeness of the exposure scenarios considering the broad spectrum of general rubber good and the limited knowledge of their composition. Considering the hazardous properties for human health and the associated risks following exposure of DPG, relevant regulatory management options for consumer’s exposure are considered.

## Identification and assessment of risk management options

### CLP regulation: Harmonised Classification

As indicated in section 1.4.1, a revision to include Repr. 1B, H360fd, Skin Sens. 1A H317 and STOT RE 2, H373 of the harmonised classification is ongoing. No additional need for a classification of DPG as endocrine disruptor was identified in this RMOA document.

A harmonised classification leads to a formal recognition of hazardous properties and better information of users. The upcoming, revised harmonised classification will confirm the hazardous properties of DPG to enable a proper risk management and choice of the appropriate RMM.

According to Art. 22 paragraph 1 f) of REACH, Registrants are obliged to update their substance registration information at any change in the classification and labelling of the substance. Further, any actor in the supply chain of a substance or a mixture shall communicate new information on hazardous properties (Art. 34 a).

A harmonised classification Repr. 1B have impact through downstream regulations:

At the workplace, determination of hazardous properties is part of the obligatory risk assessment under worker legislation (98/24/EC, Art. 4). The risk assessment under worker legislation clearly benefits from harmonised classification of hazardous properties under CLP. Directive 98/24/EC (CAD) set general obligation for prevention of chemical risks. More stringent rules applies for CMR substances for which Directive 2004/37/EC (CMRD) specifically set the hierarchy of RMM (known as S-T-O-P principle), which needs to be followed, with the preference for substitution, then technical or organisational measures and PPE at last.

In relation to the use of DPG in articles, the European directive 2009/48/CE prohibited the use of carcinogenic, mutagenic or toxic for reproduction (CMR) of category 1A, 1B or 2 under Regulation (EC) No 1272/2008 substances in toys, in components of toys or in micro-structurally distinct parts of toys intended for use by children when present above classification generic concentration limits. It is noted that provisions of the Toy Directive already apply to CMR 2 such as DPG. The CSR states that DPG is not allowed in toys used by children under 36 months. However, such ban was not identified in the directive 2009/48/CE by the aMSCA. The CSR includes scenario with use of balloons by children above 36 months. It is indicated that DPG is expected in GRG at a concentration of 0.23%. This concentration is below the Repr. 2 and Repr.1B generic concentration limits.

In addition, the Commission requested ECHA to prepare an investigation report (ongoing 2023) to support the preparation of a restriction proposal on the use of CMR 1A or 1B substances in childcare articles (CCA) on the basis of Article 68(2) of REACH. In the mandate from the Commission, CCAs are defined as follows:

a) articles under the definitions in entry 51 of Annex XVII of REACH:

any product intended to facilitate sleep, relaxation, hygiene, the feeding of children or sucking on the part of children.

b) and/or articles within the remit of CEN TC 252:

any product designed or obviously intended to safely ensure and facilitate seating, bathing, changing and general body care, feeding, sleeping, transportation and protection of young children.

Thus, a harmonised classification as Repr. 1B could enable to prohibit a certain amount of articles containing DPG to the children, a vulnerable groups to the risks caused by chemical exposure.

Besides, a classification of DPG as Skin Sens. 1A, H317 is proposed. The harmonised classification entails legal requirements, such as labelling to inform users of substances and mixtures about their safe use. Precautionary statements (P280) highly recommend to wear protective gloves or clothing, eye protection or face protection. The labelling requirement, however, does not cover articles such as clothing, bedlinen or footwear. A restriction proposal on skin sensitising substances in textile, leather, fur and hide is currently under consideration by the European Commission. This restriction stipulates that substances newly classified as category 1/ 1A / 1B allergens in Annex VI of the CLP Regulation will become subject to the restriction within 3 years after their official classification date. As the extent of articles where DPG is present is unknown, there is a possibility that DPG might be present in textile and would be subject to this restriction. The concentration limit proposed for textiles is 130 mg/kg.

### REACH Regulation

#### Authorisation: Identification as SVHC/Candidate Listing without Inclusion in Annex XIV

Further to the revision of its harmonized classification as Repro 1B, DPG will qualify for identification under Article 57(c) as SVHC (substances meeting the criteria for classification in the hazard class reproductive toxicity category 1A or 1B, adverse effects on sexual function and fertility or on development in accordance with section 3.7 of Annex I to Regulation (EC) No 1272/2008).

While Candidate Listing is often seen as a first step to authorisation, it has direct effects even when the substance is not yet included in Annex XIV.

Most importantly, Candidate Listing triggers information rights for consumers and the duty to report certain information for industry:

Requirement to inform customers and consumers under REACH (Art. 33):

Suppliers of articles which contain DPG in a concentration above 0.1 % (w/w) have to provide sufficient information to allow safe use of the article to their customers within the supply chain. Additionally a consumer can request such information from the supplier as well and it has to be provided within 45 days after the request.

Requirement to notify ECHA under REACH (Art. 7(2)):

Producers or importers of articles containing DPG in a concentration above 0.1 % (w/w) have (under certain conditions) to notify ECHA that their article contains a substance on the Candidate List. This obligation applies if the substance is present in those articles in quantities totaling over one ton per producer or importer per year.

In addition, this information is published in the open SCIP database (database for information on Substances of Concern In Articles as such or in complex Products) established under the Waste Framework Directive (2008/98/EC) to make the information available to waste operators and consumers. This information would also trigger an obligation for the Registrants to notify the presence of DPG in articles containing a concentration above 0.1% and help reduce the information gaps related to the lack of available data regarding the article containing DPG.

SVHC identification as such is considered to encourage the substitution of the substance. In several industrial supply chains specific conditions of purchase are already in place for substances of concern. These conditions might include terms like “absence of SVHC in the delivered product” with thresholds for residual SVHC lower than the regulatory triggers. The above mentioned obligations for suppliers and importers of DPG as a substance itself, mixtures and articles containing DPG, might support to pave the way for a reduction of human exposure and emissions of DPG into the environment by promoting substitution with less hazardous substances or alternative techniques.

However, an SVHC identification would not be any obligation to substitute DPG. The Candidate Listing might support reduction of human exposure and emissions to the environment to a certain extent but is not seen as an effective risk management tool to address risks, if relevant.

#### Authorisation: Identification as SVHC/ Candidate listing with inclusion in Annex XIV

A prerequisite for a substance to be included on the Annex XIV of REACH is to be identified as a SVHC. Once listed on the Annex XIV, its continued use, beyond an agreed sunset date, will only be allowed if the substance has been authorised for a specific use. Application for authorisation are scrutinized by the ECHA committees RAC and SEAC and finally granted by the European Commission. Some of the uses may be exempted from authorisation requirements.

The prioritisation for inclusion in Annex XIV from the candidate list is based on hazard (triggered by SVHC identification) and consideration of tonnage and types of uses. Priority is driven by several criteria that are set by Article 58 of REACh. The aMSCA considers that the substance meets the criteria for classification in the hazard class reproductive toxicity category 1B. DPG is produced or imported into the EU in volumes of 10,000 – 100,000 tpa. Considering ECHA prioritisation (ECHA, 2014), it is assumed that for DPG a relatively high score might be assigned. Whether this score is sufficient for a prioritisation of DPG for inclusion in Annex XIV, would further depend on the assigned scores of all other substances in the Candidate List in a particular prioritisation round.

Authorisation addresses the use of a substance as such as well as in mixtures and would cover industrial and professional uses of the substance. The uses of DPG and in particular the incorporation of DPG into an article, e.g. tyres, would be subject to the authorisation requirement. In this case the risks for human health during production and professional uses has to be addressed in an application for authorisation. Authorisation might lead to a total reduction of the use of DPG and might increase R&D efforts to replace DPG with less hazardous substances (or with technical or functional alternatives).

However, articles which are imported into the European Union will not be covered by these obligations. The placing on the market (either produced in the EU or imported) and the use of an article which contains DPG is not a subject of the authorisation process. In addition, authorisation will be considered on in relation to the SVHC property of DPG, i.e. in relation to human health. Therefore, this measure would not have any direct impact on health risks from imported articles and on environmental risks.

#### Restriction

Restriction shall address an unacceptable risk to human health or the environment arising from the manufacture, use or placing on the market of substances (Art 68). This option may also cover articles, imported or manufactured in the EU. A restriction can be scoped in different ways: either as general restriction covering all products which contain DPG above a certain concentration, or as a restriction to cover relevant exposure/emission sources from specific uses for which unacceptable risks for environment or human health were identified.

Although an Annex XV restriction proposal would show several advantages over the REACH authorisation procedure (e.g. may cover the risks for the environment and risks related to the use of articles), an “unacceptable risk has to be demonstrated”.

The aMSCA considers a restriction under REACH as a disproportionate measure at this point in time. In relation to risks for human health, the aMSCA recommend that registration dossiers are updated considering the DNEL as described in section 2.1.1 to provide demonstration that risks are adequately controlled for all registered uses of the substance. Considering the low magnitude of risks, refinement of exposure assessment with Tier II tools and addition of RMM may result in refinement and possibly control of risks.

To strengthen the implementation of RMM according to the S-T-O-P principle and protect workers, setting of OELs appears to be an appropriate way of regulation. In case further risks for the workers are identified by authorities after the updates of registration dossiers, the option of a restriction under REACH might be reconsidered.

In relation to risks to the environment, risk management measure on the industrial sites (i.e. zero release of DPG as claimed by one of the registrant) might be sufficient to cover the unacceptable risks. Monitoring and enforcement should be made to identify the release and exposure to the environment coming from the manufacture and formulation sites. In addition, the uncertainties related to the release of DPG from articles produced in Europe but also from imported article, and the exposure scenario related to the transformation of these products needs to be cleared up. If risks from imported articles are relevant, a restriction proposal would be an appropriate measure. Thus the identification of specific uses of DPG relevant for a restriction proposal might be further reconsidered.

Finally, the possibility of substitution and alternatives also needs to be considered to decide on the appropriateness of this management measure.

### Occupational exposure limit (OEL) value under worker legislation

Occupational exposure limits (OELs) are regulatory values which indicate levels of exposure that are considered to be safe (health-based) for a chemical substance in the air of a workplace. In the perspective of addressing the risks demonstrated for workers exposed to DPG, setting binding OELs within the framework of the CMRD (Directive 2004/37/EC)[[12]](#footnote-13) would be an option that would allow a harmonized measure within the EU and would oblige the Registrants to comply with the requirements and to prevent workers exposure. The aMSCA considers that the substance meets the criteria for classification in the hazard class reproductive toxicity category 1B and the limits values are set by regulatory authorities at EU and national levels, taking into account the available information and most recent data on the hazards of a substance, particularly with respect to carcinogenicity, mutagenicity, toxicity to reproduction. Such limit values set by CMRD are binding and shall be transposed in national laws by each Member States either with the same or with more restrictive values. This ensures harmonised implementation within Member States without imbalance both for Industry’s competition and workers protection.

Health protection of workers exposed to chemical substances is based on two complementary methodologies to assess the exposure: air monitoring and biological monitoring. As indicated in ECHA website[[13]](#footnote-14): “OELs are mainly intended to prevent workers from inhaling chemicals as vapours, mists or dusts. However, RAC may also provide recommendations for a skin notation indicating that dermal protection is needed. Other notations for sensitisation or noise are also possible. Additionally, RAC may recommend biological limit values (BLVs - biomonitoring exposure levels) or biological guidance values (BGVs - biomonitoring background levels). Considering that dermal exposure is an important route of exposure for DPG, setting of BLV or BGV should be considered for DPG.

As stated in both CAD and CMRD, priority should be given to avoid exposure and it may be anticipated that companies would implement more stringent on-site RMMs. Drivers for substitution are not mandatory for CAD and to be undertaken ‘if technically possible’ for CMRD.

In conclusion, Directive 2004/37/EC on carcinogens, mutagens or reprotoxic substances at work is considered consistent with the objective stated above. Indeed, it would, depending on the value agreed on, generally decrease the accepted exposure level at the EU level. Stricter measures could be decided later on if needed, based on results from on-site surveys and national controls. Nevertheless, setting OELs does not automatically lead toward the substitution of a CMR substance.

### Emission limit for DPG in water

The assessment of exposure and risks characterization has identified a need to consider further regulatory action to reduce the emission of DPG to the aquatic environment.

The revised **Drinking Water Directive** (Directive 2020/2184/EC on the quality of water intended for human consumption)[[14]](#footnote-15) aims to protect citizens and the environment from the harmful effects of contaminated drinking water and to improve access to drinking water. In relation to its capacity to contaminate drinking water resources, in particular due to the release of DPG from articles (water pipes), DPG might be addressed within the DWD. The revised Directive aims at:

- reinforcing water quality standards, in line or, in some cases, even more stringent than the World Health Organisation (WHO) recommendations;

- tackling emerging pollutants, such as endocrine disruptors and PFAs, as well as microplastics;

- a preventive approach favouring actions to reduce pollution at source by introducing the risk-based approach;

- harmonising the quality standards for materials and products in contact with water.

Under this directive (DWD), the European Commission is preparing a European positive lists of starting substances, compositions and constituents which will be authorised for use in the manufacture of materials or products in contact with drinking water (DW), including expiry dates and, if appropriate, conditions of use and migration limits in DW. According to article 11 of DWD, the first positive list should be adopted in 2025, and the requirements for DPG in this context is unknow. In this framework, substances that have a harmonised classification as CMR Cat. 1A or 1B according to Annex VI to the CLP Regulation should be considered to be the highest priority for review.

Further, the drinking water legislation would request all drinking water suppliers to control DPG concentrations at the tap, but not limit the concentration of the substance in the resources of the drinking waters. This would mean both, that the resources are protected inadequately, and that drinking water facilities might have to find solutions of removing DPG from drinking water without being the source of the DPG emission. In this case the costs for remediation of DPG from the raw water are transferred to the society whereas the polluters are not obliged to contribute to the remediation costs. In addition, this RMM will not be effective to reduce the risks for environment.

Considering, the risks for the aquatic environment on a local scale from industrial activities linked to DPG, its potential M/vM properties which can lead to a diffusion of the substance and contamination of water resources, and its ubiquitous presence in the environment most likely related to tyres abrasion, DPG could be considered in the **Water Framework Directive** (WFD) for community action in the field of water policy (2000/60/EC). However, for this regulation to be applicable to all Member States, DPG would have to be on the list of priority substances in the field of water (appendix X of the WFD), which is not the current case. The substance might be included in the list of priority substances of the WFD if:

- Sufficient data is available, covering almost all Member States;

- It is taken into account in the prioritization carried out by the JRC;

- It is prioritized;

- It is retained by the Member States and the Commission.

The integration of DPG in the appendix X of this directive would allow to:

- introduce monitoring of DPG in waters;

- limit the contamination of environments by setting a limit value that takes into account the risks for the aquatic environment;

- protect water resources for the production of water intended for human consumption;

- provide means of action to limit emissions at the local level.

Since the entry into force of the directive, a watch list has been set up in France[[15]](#footnote-16) and Europe[[16]](#footnote-17). To date, DPG is not on any of these watch lists. The substances appearing on this watch list must be selected from among those for which the available information indicates that they may present a significant risk, at European Union level, for or via the aquatic environment, but for which the monitoring are insufficient to reach a conclusion on the actual risk posed.

Finally, this directive would make it possible to establish an environmental limit value making it possible to regulate the discharges from the installations (of industries manufacturing DPG, or GRG and tyres, for example).

The **Industrial Emissions Directive** (IED Directive 2010/75/EU) aims to achieve a high level of protection of human health and the environment taken as a whole by reducing harmful industrial emissions across the EU and could be considered as a complementary risk management option. Regarding the risks for the environment, releases of DPG, in particular due to industrial emissions, could be regulated by defining emission limit values. By applying such an approach, two important risk management principles would be followed: the upstream limitation of releases, and that the burden relies on the companies responsible for the source of emission. Defining stringent release concentrations of DPG and including suitable emission monitoring requirements could be of added value to control environmental emission of DPG. In addition, this directive takes into account the local conditions at industrial sites i.e. the geographical location or the local environmental conditions of the installation concerned.

On that particular point, the aMSCA considers that the emphasis should be put on the temporal variation of the water flow and the emission releases in periods of scarcity of the resource. The aMSCA also considers that the monitoring data provided in the course of a chemical safety report and use for assessment has a limited lifetime. This is particularly important in times of extreme environmental variability.

Synthesis of applicable risk management options

**Table 9: Summary of concerns and applicability of risk management options**

|  |  |  |
| --- | --- | --- |
| **Critical hazard/risks** | **Characterisation** | **Applicable RMM** |
| Critical hazard for human health | * Reproductive toxicity * Neurotoxicity * Skin sensitisation | * Harmonised classification ongoing * SVHC identification and potential inclusion in Annex XIV applicable when classified Repro 1B |
| Widespread presence in water | * Low risk identified based on available monitoring data | * Further monitoring recommended * Water Framework Directive |
| Risk for the environment related to manufacture, industrial and professional uses of DPG | * Risks identified for water and sediments if not covered by on-site RMM | * Registration dossiers to be updated * Industrial Emission Directive |
| Risk for the environment related to tyre use | * Not evaluated in registration dossier * Monitoring: ubiquitous substance, few data indicating risk for the aquatic species * Uncertainties related to the low amount of data | * SVHC identification would trigger an obligation to notify the presence of DPG in articles and improve knowledge on the extent of exposure |
| Risk for industrial workers | * Risks identified based on scenario in registration dossier and revised DNEL by aMSCA | * Registration dossiers to be updated * Classification Repr 1B may further strengthen RMM * OEL would improve worker protection * Restriction and/or authorisation to be considered if needed |
| Risk for occupational workers | * Risks identified based on scenario in registration dossier and revised DNEL by aMSCA | * Registration dossiers to be updated. * Classification Repr 1B may further strengthen RMM * Restriction to be considered if needed |
| Risks for consumers due to the use of articles | * Risks identified based on scenario in registration dossier and revised DNEL by aMSCA * Uncertainties on the extent of articles in which DPG can be present | * Presence of DPG in Toys banned for classification as repro 1 and 2 * SVHC identification would trigger an obligation to notify the presence of DPG in articles and improve knowledge on the extent of exposure * Restriction to be considered if needed |
| Risks for consumers due to presence in drinking water | * Presence of DPG in drinking water plant * Release of DPG from material in contact with water (pipes and tubes) * Uncertainties related to the low amount of data | * Drinking Water Directive |

The eMSCA noted the limitations in this dossier related to the lack of essential data on, for example, the presence of DPG and other by-product in articles. On the other hand, the presence of the substance in the environment and the multiple exposure pathways are unequivocal. Altogether these contradictory information confirm a concern that cannot be efficiently resolved by current regulatory tools, especially for the consumers.

# Conclusions and actions

To be developed at a later stage (after public consultation).

# Annex I: Background document

# Information on uses

**Table 10: Overview of uses according to ECHA dissemination site (non-exhaustive list)[[17]](#footnote-18)**

|  |  |
| --- | --- |
|  | **Use(s)** |
| **Manufacture** | Manufacture of the substance and Production of tyres (including manufacturing, retreating, service life and end of life)  PROC 2, 3, 5, 8a, 8b, 9, 10, 13, 14, 15, 21, 22, 24 |
| **Formulation** | Masterbatches manufacture  PROC 1, 8b, 9, 14, 15, 21, 24  Masterbatch production - internal mixture  PROC 5, 8a, 8b, 9, 14  Masterbatch manufacture-continuous process  PROC 1, 8b, 9, 14, 15, 21  Formulation and re-packing of substances and mixtures  PROC 1, 2, 3, 4, 5, 8a, 8b, 9, 14, 15  Formulation and re-packaging  PROC 5, 8a, 8b, 9  Production of tyres and general rubber goods  PROC 1, 2, 3, 4, 5, 6, 8b, 9, 10, 13, 14, 19, 21, 24  Production of tyres (including manufacturing, retreating, service life and end of life)  PROC 2, 5 8a, 8b, 9, 10, 13, 14, 21, 22, 24  End of Life tyre: Coarse shredding  PROC 8a, 8b, 21  End of life Tyre: Grinding (ambiant)  PROC 8a, 8b, 24  End of Life Tyre: Grinding cryogenic  PROC 8a, 8b, 24  End of Life Tyre: Pyrolysis  PROC 2, 8b, 22  End of Life Tyre: Energy recovery: cement kiln  PROC 8b, 21, 22  End of Life Tyre: Energy recovery: other  PROC 8b, 21, 22  End of Life Tyre: Electric arc furnace  PROC 8b, 21, 22  End of Life Tyre: Devulcanization/reclaim  PROC 8b, 21, 22 |
| **Uses at industrial sites** | Use in lubricants and lubricant additives  PROC 1, 2, 3, 4, 7, 8a, 8b, 9, 10,13, 17, 18  Production of tyres (including manufacturing, retreating, service life and end of life)  PROC 2, 5 8a, 8b, 9, 10, 13, 14, 21, 22, 24  Pre-step tyre – manufacturing and handling of DPG grad GC  PROC 5, 14, 21  Manufacture of General Rubber Goods - According to ETRMA  PROC 5, 8b, 9, 10, 13, 14, 21  Manufacture of Tyres - Production and Retreading - According to ETRMA  PROC 5, 8b, 9, 10, 14, 21  Manufacuring of substance (industrial application)  PROC 2, 3, 5, 8b, 9, 14  Mixing  PROC 5, 8b, 9  Cement preparation  PROC 9  Production of general rubber goods (GRG)  PROC 5, 8b, 9, 10, 13, 14, 21  Production of tyres and general rubber goods  PROC 1, 2, 3, 4, 5, 6, 8b, 9, 10, 13, 14, 19, 21, 24  Use in formulations for coatings, adhesives, binders and sealants  PROC 3, 7, 8a, 8b, 9, 10, 13, 23  Final treatment  PROC 10, 21  Use in formulations for building and road constructions  PROC 3, 8a, 8b, 23  Weighing  PROC 9  Curing  PROC 14  Use as laboratory agent  PROC 15  Shaping  PROC 10, 13, 14, 21  Storage  PROC 8b, 9  Importation and storage  PROC 8b |
| **Uses by professional workers** | Tyre mounting and dismounting and handling of technical rubber goods  PROC 21  Retreading and recycling  PROC 10, 14, 21  Use in formulations for building and road construction  PROC 8a, 8b, 23  Use in formulations for coatings, adhesives, binders and sealant  PROC 8a, 8b, 9, 10, 11, 13, 15, 15, 23  Use in lubricants and lubricant additives  PROC 1, 2, 3, 4, 8a, 8b, 10, 11, 13, 17, 18, 20 |
| **Consumer uses** | Use of tyres and general rubber goods  ERC 10a, 10b, 11a |
| **Article service life** | Tyre service life  PROC 21  ERC 10b  AC 10  Service life (Use of general rubber goods by consumers)  PROC 21  ERC 10a  AC 10  Service life (professional workers)  PROC 21  ERC 10a, 10b  AC 10  Tyre mounting and dismounting and handling of technical rubber goods  PROC 21  ERC 10a, 11a  AC 1, 2, 3, 10  Garage owner-tyres change  PROC 21  ERC 10a, 11a  AC 1  Retreading and recycling  PROC 10, 14, 21  ERC 10b, 11b  AC 1, 2, 3, 10  GRG articles - conveyor belt  PROC 21  ERC 11a  AC 10a  End of Life Tyre: ELT pre-processing storage  PROC 21  ERC 10a, 11a  AC 1  ELT articles - installation of shock absorbing tiles  PROC 21  ERC 10a, 11a  AC 1  ELT articles - installation of synthetic turf fields  PROC 21  ERC 10a, 11a  AC 1  Road repair  PROC 8a, 8b, 23  ERC 8c, 8f, 10a  AC 0  Use of tyres and general rubber goods  ERC 10a, 10b, 11a  AC 1, 2, 3, 10  Consumer use of tyres (vehicles)  ERC 10a  AC 10  GRG articles (balloons) – consumer  ERC 10a, 11a  AC 10a, 10b  ELT articles - shock absorbing tiles (children < 3 years)  ERC 10a, 11a  AC 10a  ELT articles - synthetic turf fields (children < 6-11 years)  ERC 10a, 11a  AC 10a |

# Hazard Information

## Hazard assessment

### Setting of DNELs considering the recent EOGRTS study

1,3-diphenylguanidine (DPG) full toxicological profile is available in ANSES conclusion document on substance evaluation published in ECHA disseminated website (ANSES, 2020)[[18]](#footnote-19).

DPG was included in the Community rolling action plan (CoRAP) for evaluation in 2012 by France according to REACH regulation. Based on the evaluation of the available data, it was concluded that all the hazard concerns identified were covered, with the exception of reproductive toxicity. During substance evaluation, a data gap was identified for this substance according to REACH annex X, section 8.7.3 covering adverse effects on the full range of reproductive endpoints. A decision on compliance check under REACH regulation was sent to the Registrants on 22 March 2019 by ECHA to request an EOGRTS, the study was received in July 2021. In 2020, ANSES published a substance evaluation conclusion and evaluation report on DPG as required by REACH Art. 48. The report was prepared based on the REACH registration and literature available at that time, without including the EOGRTS. DNEL calculations were performed based on the available studies. It was stated that the revision of the current DNEL would be necessary after reception of the EOGRTS study.

In the context of SEv and accounting for the absence of chronic toxicity study, the selection of the critical DNELs for DPG (pending upcoming EOGRTS study) were based on sub-chronic toxicity for systemic effect (long-term). The critical effects observed in a 90-day toxicity study in rats regarded haematological and clinical chemistry and a NOAEL of 11 mg/kg bw was identified for DNEL calculation.

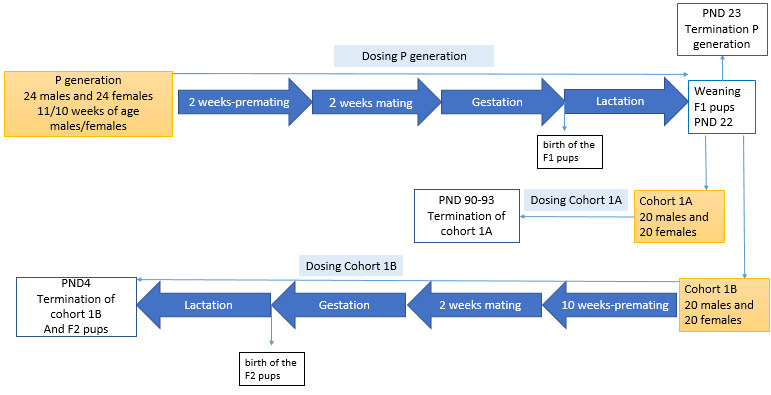
**Table 11: Selection of the critical DNELs for DPG as indicated in SEv conclusion document (Anses, 2020)**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Critical DNELs/DMELs** | | | | |  |  |  |
| **Endpoint of concern** | | **Type of effect** | | **Critical study(ies)** | **Corrected dose descriptor(s)**  **(e.g. NOAEL, NOAEC)** | **DNEL/ DMEL** | **Justification/**  **Remarks** |
| Sub-chronic toxicity  Systemic effect-Long-term | 90-day toxicity study | | NOAEL = 11 mg/kg bw | | NOAEL | Inhalation:  0.16 mg/m3  Dermal:  1.1 mg/kg bw | Workers |
| Sub-chronic toxicity  Systemic effect-Long-term | 90-day toxicity study | | NOAEL = 11 mg/kg bw | | NOAEL | Inhalation:  0.032 mg/m3  Dermal:  0.16 mg/kg bw  Oral:  0.016 mg/kg bw | General population |
| Reproductive toxicity | No DNELs: datagap need to be addressed first | | | | | | |
| Skin sensitisation | No quantitative DNEL could be derived. Nevertheless, classification of the substance is needed as a RMM for this endpoint of concern. | | | | | | |

Analysis of the EOGRTS study OECD TG 443: critical effect and selection of point of departure for DNEL setting

The new EOGRTS requested during the evaluation was assessed by the aMSCA. The study was conducted according to OECD TG 443 and is GLP compliant (Unpublished study report, 2021). The study is considered valid with a Klimisch score of 1. A summary table of the EOGRTS study is available in section 2.1.3.

In this study, Sprague-Dawley rats were exposed by gavage to doses of 5, 15 and 25 mg/kg bw/d of DPG (with 0.5% aqueous methylcellulose). The study design is presented below:



**Figure 1: Study design of the EOGRTS based on oral gavage of DPG (Unpublished study report, 2021)**

DPG displayed effects on fertility and sexual functions as well as effects on the development of the offspring. Effects are detailed in section 2.1.3.and the main effects are described below.

**Regarding general toxicity:**

There were no adverse effects during the premating, mating, gestation or lactation periods associated to the mean body weight, mean body weight change and mean food consumption for parental generation and cohort 1A and 1B.

Clinical signs suggestive of neurologic disorders (e.g clonic convulsion, locomotor difficulties, loss of balance, staggering gait and/or tonic seizures) were seen in females of the high dose group (25 mg/kg bw/d) only at the end of the pregnancy period. Maternal toxicity including neurotoxicity was not observed at dose levels below 25 mg bw/kg in both generations.

Results of splenic lymphocyte subpopulation analysis in cohort 1A indicated statistically significant increase of NK cells at 15 mg/kg bw/d in males. In females and when compared to the controls, there was a statistically significant decrease of NK cells at 25 mg/kg bw/d.

Increased liver weights (relative to body) were recorded in males and females treated at 15 mg/kg bw/d (p<0.01) in P generation. Statistically significant increased liver weights (relative to body) were recorded in females treated at ≥ 5 mg/kg bw/d and in males treated at 25 mg/kg bw/d in cohort 1A. Finally, increased liver weights (relative to body weight) were recorded in males at ≥ 15 mg/kg bw/d (p<0.01) and absolute liver weight increase in females treated at ≥ 15 mg bw/kg bw/d in cohort 1B.

**Regarding adverse effects on sexual function and fertility:**

In the parental (P) generation, effects on the duration of phases of the estrous cycle were recorded. A dose-related decrease of mean number of days of metestrus was observed from 15 mg/kg bw/d (p<0.05) as well as an increase of mean number of days of estrus at 25 mg bw/kg bw/d (p<0.01).

In the cohort 1B (F1 generation), a statistically significant increase of the mean duration of gestation was observed at 25 mg/kg bw/d (p<0.05).

Dystocia was observed in both generations: one pregnant female in the P generation at 15 mg bw/kg and another one at 25 mg/kg bw/d, and one pregnant female in cohort 1B at 25 mg/kg bw/d.

**Regarding effects on the development of the offspring:**

In P generation, a statistically significant increase of post-implantation losses was noted at 25 mg/kg bw/d (p<0.05). No statistically significant effects were observed for cohort 1B.

The number of dead, missing or cannibalized pups at post-natal day (PND) 1 to 4 was significantly increased and dose-related in P generation from 5 mg/kg bw/d (p<0.01) and from 15 mg/kg bw/d (p<0.001) in F1 generation. The mean number of live pups on PND 1 was not significantly affected in P and F1 generations. A significant lower mean number of viable pups on PND1 was however recorded in cohort 1B at 25 mg/kg bw/d (p<0.01).

At 25 mg/kg bw/d, on PND 1, body weights of F1 and F2 pups were decreased compared to controls with statistical significance in males (p<0.01). The body weight returned to control values thereafter.

Thus, the effect on the survival of pups during lactation between PND 1 to 4 in the F1 and F2 pups was considered as a critical effect in this study.

**Indeed, a statistically significant increase of mortality of F1 and F2 lactating pups was observed during PND 1 to 4, from 5 mg/kg bw/d in F1 and 15 mg/kg bw/d in F2.**

**Table 12: Measured effect on the development of the offspring-mortality**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Number of dead, missing and/or cannibalized pups at PND 1 to 4 (%) | | | |
| Doses (mg/kg bw/day) | 0 | 5 | 15 | 25 |
| F1 pups | 14 (4.9) | 35 (12.5)\* | 47 (16.2)\*\* | 82 (32.3)\*\* |
| F2 pups | 2 (1.0) | 8 (3.4) | 56 (24.2)\*\* | 73 (37.4)\*\* |

Statistical significance: \*(p<0.01) \*\*(p<0.001)

**Other effects were considered as supporting data for reproductive toxicity, as they are consistent with the effects observed above but no statistical significance was attained.**

A trend toward increased gestation period on an individual basis was observed in the P generation from 5 mg/kg bw/d.

A tendency toward a lower live birth index was recorded from 5 mg bw/kg bw/d in cohort 1B.

A tendency toward an increase in post-implantation losses was seen in cohort 1B from 5mg/kg bw/d.

In addition, two females developed an adenocarcinoma in mammary gland, in the parental generation and in the F1 generation, at 5 mg/kg bw/d for the P and 25 mg/kg bw/d for the cohort 1B. There is no information to conclude if this effect was spontaneous or linked to the treatment.

A LOAEL of 5 mg/kg bw/d was established and, thus, a NOAEL < 5mg/kg bw/d for both fertility and developmental effects based on F1 pups mortality.

DNEL derivation

The OECD TG 443 study is considered a key study for reproductive toxicity and the effects observed were considered relevant for DNEL derivation. Indeed, significant pups mortality was observed in F1 lactating pups from 5 mg/kg bw/d during PND1 to 4. The same tendency was recorded in F2 lactating pups with statistical significance at the mid dose. Considering the severity of this effect and its statistically significance at the lowest dose in F1, it was considered as the critical effect, and the LOAEL of 5 mg/kg bw/d as Point of Departure (PoD) for the calculation of the Derived no effect level (DNEL) for reproductive toxicity of DPG.

Assessment factors are applied in accordance to ECHA guidance document R8(ECHA, 2012), and are summarized in Table XXX and YY below:

**Table 13: Summary of the assessment factors used in DNEL derivation for workers**

|  |  |  |
| --- | --- | --- |
| **Starting point** | **Dermal** | **Inhalation** |
| Correction for absorption | 10% | 100% |
| Corrected starting point | 5 mg/kg bw/d x (7d/5d) : 10%  **70 mg/kg bw/d** | 5 mg/kg bw/d x (7d/5d) x (1/0.38m3/kg/d) x (6.7m3/10m3) : 100%  **12.3 mg/m3** |
| **Assessment factors- accounting for differences in:** | **Dermal** | **Inhalation** |
| Intraspecies factor | 5 | 5 |
| Exposure duration | 1 | 1 |
| Dose response/severity | 5 | 5 |
| Data base quality | 1 | 1 |
| Total assessment factor | 250 | 62.5 |

As evaluated in the Conclusion document (Anses, 2020), inhalation and oral absorption were considered 100% by default. A study conducted by Shah et al. (1985) demonstrated that DPG is slowly absorbed after dermal application to rats (around 10 % in rats). Thus, dermal absorption was considered 10% by default.

Rats in the study are exposed 7/7 days whereas workers are exposed 5/7 days. An adjustment factor of 7/5 was added to correct the LOAEL for dermal and inhalation routes.

To establish the inhalation DNEL in workers, R8 guidance criteria were applied to correct the oral LOAEL based on a correction of respiratory volume for the relevant duration: for a 8h of exposure, the respiratory volume of rats and humans are 0.38 m3/kg bw/d and 6.7 m3, respectively. The worker respiratory volume for light activity (8h exposure) is 10 m3/person.

**Table 14: Summary of the assessment factors used in DNEL derivation for consumers**

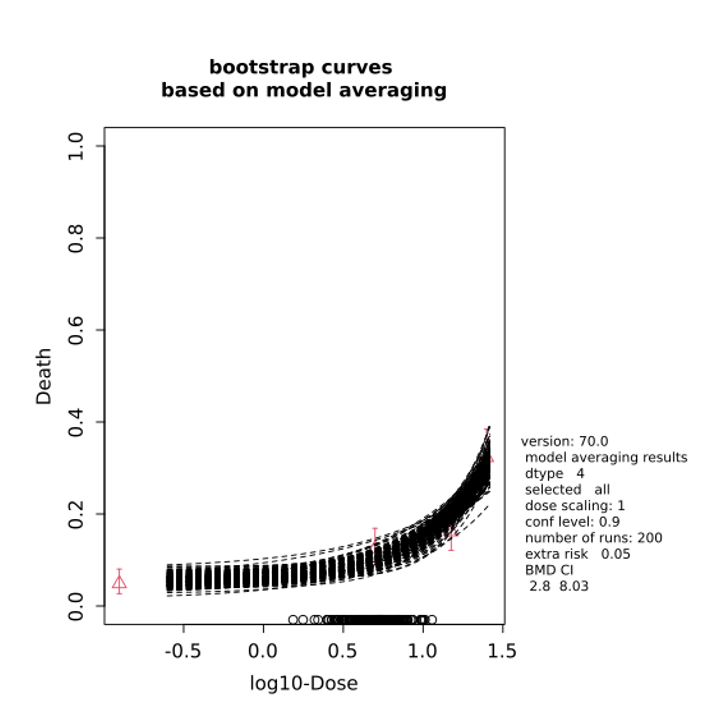
|  |  |  |  |
| --- | --- | --- | --- |
| **Starting point** | **Dermal** | **Inhalation** | **Oral** |
| Correction for absorption | 10% | 100% | 100% |
| Corrected starting point | 5 mg/kg bw/d : 10%  **50 mg/kg bw/d** | 5 mg/kg bw/d x (1/ 1.15m3/kg/day) : 100%  **4.35 mg/m3** | **5 mg/kg bw/d** |
| **Assessment factors- accounting for differences in:** | **Dermal** | **Inhalation** | **Oral** |
| Remaining differences | 2.5 | 2.5 | 2.5 |
| Interspecies factor | 4 (rat, allometric scaling) | - | 4 (rat, allometric scaling) |
| Intraspecies factor | 10 | 10 | 10 |
| Exposure duration | 1 | 1 | 1 |
| Dose response/severity | 5 | 5 | 5 |
| Data base quality | 1 | 1 | 1 |
| Total assessment factor | 500 | 125 | 500 |

To establish inhalation DNEL in consumers, R8 guidance criteria were applied to correct the oral LOAEL based on a correction of respiratory volume for relevant duration: for a daily exposure, the respiratory volume of rats is 1.15 m3/kg bw/d.

As recommended in the R8 guidance document (ECHA, 2012), the choice of a specific assessment factors in relation to qualitative and quantitative uncertainties should be decided on a case-by-case basis. The recommendations for specific assessment factors are given as intervals in the guidance document with the intention that the risk assessor should evaluate all available information on a case-by-case basis and justify the choice of the assessment factor. It is proposed that, when the starting point for the DNEL calculation is a LOAEL, an assessment factor (dose-response assessment factor) ranging from 3 (as minimum/majority of cases) to 10 (as maximum/exceptional cases) is applied. As mentioned in R8 document, the factor retained should consider the dose spacing in the experiment, the shape and slope of the dose-response curve, and the extent and severity of the effect seen at the LOAEL.

**Slope of the dose-response:**

When considering the data for F1 pups mortality, it is noticed that the slope of the dose-response curve is shallow, which gives uncertainty about the statistical derivation of the NOAEL. The R8 guidance document mentions that the benchmark dose (BMD) approach is an alternative of the default assessment factors used in human health risk assessment for the dose response curve and, when possible, is preferred over the LOAEL NOAEL extrapolation. A BMD calculated as the lower confidence limit of the dose that produces a response of 5% (BMD5) has, on average, been proposed to be comparable to a NOAEL (WHO, 2000). This approach was considered in the aMSCA assessment. The BMR (benchmark dose response) with an extra risk of 5% compared to the controls for the pups of the F1 generation was used. Results were obtained using the EFSA web-tool for BMD analysis, which uses the R-package PROAST (v. 70.0) for the underlying calculations.



**Figure 2: Bootstrap curves based on model averaging results (200 runs, extra risk 0.05, BMD 2.8 CI 8.03)**

F1 BMDL results of 2.85 mg/kg bw/d was obtained. However, an alert on AIC results while running the program, suggests that the use of the BMD approach might not be considered as an appropriate basis for DNEL derivation. One hypothesis for this alert could be that the data containing the litter effect, which is only statistically significant at the higher dose, were not taken into account.

**Table 15: Measured values indicating of the litter effect**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Litter with Dead, Missing and/or Cannibalized pups, Nb. (%) (first line)  Litter with entire dead litter (second line) | | | |
| Doses (mg/kg bw/d) | 0 | 5 | 15 | 25 |
| F1 pups | 5 (21.7)  0 | 8 (36.4)  2 | 10 (45.5)  1 | 14 (60.9) \*  5\* |
| F2 pups | 2 (11.8)  0 | 2 (10.0)  0 | 13 (68.4)  2 | 17 (89.5)  4 |

Statistical significance: \*(p<0.05)

However, the BMD approach provides an alternative approach that confirms the shallow shape of the slope and the uncertainties about the statistical derivation of the NOAEL.

**Severity of the effect:**

Moreover, the R8 guidance document states that the extent and severity of the effects seen at the LOAEL in reproductive toxicity studies may, in some cases, be very marked, e.g. extensive foetal or offspring death. This should be reflected in the use of an appropriate assessment factor to account for the uncertainty related with the 'dose-response relationship'. In the study, the critical effect is a statistically significant increase in mortality of F1 lactating pups at the dose 5 mg/kg bw/d, seen during PND 1 to 4 and is a severe and irreversible effect.

In conclusion, considering the severity of the effect (mortality of pups) and the uncertainties regarding the shape and slope of the dose-response curve, an increase of the assessment factor (default factor of 3) is considered justified. Considering also that the effect is characterized from a study of good quality and of relevant statistical power, the aMSCA recommends an assessment factor of 5 for the extrapolation of the LOAEL to the NOAEL. The DNELs as calculated by the aMSCA are listed in the table below:

**Table 16: DNEL revision by the aMSCA**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Endpoint of concern** | **Type of effects** | **Population** | **Route of exposure** | **dose descriptor** | **Corrected starting point** | **Total assessment factor** | **DNELs** |
| Reproductive toxicity | Post-natal mortality of pups | Workers | Inhalation | LOAEL = 5 mg/kg bw/d | 12.3 mg/m3 | 62.5 | 0.197 mg/m3 |
| Dermal | 70 mg/kg bw/d | 250 | 0.280 mg/kg bw/d |
| Consumers | Oral | 5 mg/kg bw/d | 500 | 0.010 mg/kg bw/d |
| Inhalation | 4.35 mg/m3 | 125 | 0.035 mg/m3 |
| Dermal | 50 mg/kg bw/d | 500 | 0.100 mg/kg bw/d |

### Assessment of endocrine disrupting (ED) properties

In 2020, ANSES published a substance evaluation conclusion report on DPG based on the REACH registration and the literature available, and as required by REACH Art. 48 (ANSES, 2020). However, no conclusion on endocrine disrupting properties could have been made at that time as a datagap covering adverse effects on the full range of reproductive endpoints was identified. It was recommended to reassess the endpoint following the analysis of the requested EOGRTS study.

Reproductive and developmental adverse effects

After reception of the EOGRTS study on rats (unpublished study report, 2021), several reproductive and developmental effects raised concerns about endocrine disruption properties of DPG (see section 2.1.3 for a detailed description of the study result):

- Increase in adrenal gland weight:

A statistically significant increase in absolute and relative-to-body adrenal gland weights was observed in females at 15 and 25 mg/kg bw/d (up to +23% versus the controls) in the P generation. The total weight of the adrenal gland was considered and no data was available to discriminate if the medulla or cortical part of the adrenal glands was modified. There was no microscopic correlates. Variation was not observed in males of P generation, nor in males and females of F1 generation (Cohort 1A). This endpoint was not investigated in F2 pups.

- Effects on thyroid hormones:

A statistically significant increase of T4 concentrations (+38% versus the controls) was noticed at 25 mg/kg bw/d in P generation females. It was associated with a tendency to decrease in TSH concentrations (-10% not statistically significant).

A statistically significant decrease of T4 concentrations was observed in males of F1 generation (cohort 1A) at 5 and 15 mg/kg bw/d.

No effect on weight and histopathology of the thyroid was observed in males and females of any generation.

- Two females developed an adenocarcinoma in mammary gland; one in P generation at 5 mg/kg bw/d. This female was sacrificed moribund at the study day 40 (around 15 weeks of age); and one in the F1 generation (cohort 1B) at 25 mg/kg bw/d. This female was sacrificed moribund at the study day 97 (around 14 weeks of age).

- An increased duration of gestation was observed on an individual basis:

In the P generation, 2/22 females exposed to 5 mg/kg bw/d had a gestation duration of 24 days, associated with a high pup mortality rate. At 25 mg/kg bw/d, an increased number of females (7/24) had 23-day gestation duration (no statistical analysis was performed) when compared with 3 in the control group, associated with a high post-implantation loss. No difference was identified in the mean duration of gestation.

In the F1 generation (cohort 1B), a same trend was observed. One female over 18 exposed to 15 mg/kg bw/d, and 7/19 females exposed to 25 mg/kg bw/d had 23 days of gestation. A statistically significant increase in the mean duration of gestation was noted at 25 mg/kg bw/d (22.3 vs 21.9 in controls).

- Females presenting reproduction difficulties:

In the P generation, one female presented reddish vaginal discharge and a dead litter at 5 mg/kg bw/d. At 15 mg/kg bw/d, one female presented a dead litter and one female had dystocia with abdomen increased in size.

In the F1 generation (cohort 1B), two females treated with 15 mg/kg bw/d had dead litter. At 25 mg/kg bw/d one female had dead litters and one female presented dystocia.

No sign of neurotoxicity (e.g clonic convulsion, locomotor difficulties, loss

of balance, staggering gait and/or tonic seizures) were observed in these females in both generations.

- Post-implantation loss:

In the P generation, a statistically significant increase in the mean percent of post-implantation loss was observed in females exposed to 25 mg/kg bw/d, (27.1% vs 15.6% in controls).

In the F1 generation (cohort 1B), a tendency (non-statistically significant) for a dose-related increase in the mean percent of post-implantation loss was noted from 5 mg/kg bw/d.

- Estrous cycle alterations:

In the P generation, the EORGTS study reported a lower mean number of days spent in the metestrus stage (statistically significant) for females exposed to 15 mg/kg/day and 25 mg/kg bw/d. An increase in the mean number of days spent in the estrus phase was noticed at 25 mg/kg bw/d. No difference in the mean duration of the estrous cycle was observed in this EOGRTS study.

The same trends were observed in the F1 generation (cohort 1A) at 25 mg/kg bw/d without any statistical significance.

In an additional 90-day study on rats (NTP, 1995), Rats (F344/N strain) and mice (B6C3F strain) were respectively exposed through diet to doses of 0, 250, 500, 750, 1500 and 3000 ppm (equivalent to  0, 17/17, 32/32, 49/50, 100/95, 181/184 mg/kg bw/day in males and females rats respectively and equivalent to 0, 38/46, 75/93, 114/141, 231/285, 457/577 mg/kg bw/d in males and females mice respectively). Reproductive organs and other parameters were investigated.

In rats, at 181/184 mg/kg bw/d, decreased mean body weights were observed during the first week of the study for males and the first 2 weeks of the study for females. A high mortality was reported in this exposure group, 4/10 males survived and there was 100% mortality for females at the end of the study. At 100/95 mg/kg bw/d, a marked decrease of the mean body weight and average food consumption was observed in males and females. At 49/50 mg/kg bw/d, only a slight decrease of body weight was seen.

In B6C3F mice, no mortality was observed at all doses. At 750 ppm and 3000 ppm, the mean body weight of both sexes was lower compared to controls. Females presented a thin appearance that was also seen in males in the 3000 ppm exposure group. There was no difference on the mean feed consumption at all doses during the study.

-Estrous cycle adversity in the NTP study:

In rats, a significant increase in the length of the estrous cycle was observed for the middle dose only (50 mg/kg bw/d). This dose is two-fold higher that the maximal dose used in the EORGTS study.

In mice, the increased length of estrous cycle was statistically significant at the high dose (577 mg/kg bw/d).

Change in estrous cyclicity is an apical endpoint relevant for estrogen-mediated activity and for steroidogenesis-related activity as indicated in Revised Guidance Document 150 on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption (OECD, 2018). Therefore, this endpoint was further investigated by the Anses ED working group.

According to the OECD Guidance document for histologic evaluation of endocrine and reproductive tests in rodents part 5 (OECD, 2009), only the duration of the cycle is considered to establish whether a cycle is normal or not. An appropriate succession of the four stages of the estrous cycle, based on the well-established neuroendocrine regulation of the gonadotropic axis, is important to consider in the estimation of regular cyclicity, in particular in the control group, before any further analysis. In the EOGRTS study, only 50% of control females from the P generation had regular estrous cyclicity based on the succession of at least 2 complete cycles (around 4 days for each cycle and covering the main estrous stages) during the 15 days of monitoring. This contrasts with the study report, which concluded that 79.2% of control females had normal cycles. Thus, the data for this generation could not be used to compare the mean duration of the cycles between the experimental groups. In the F1 generation, 90% of the females were considered to have a regular cyclicity. In the exposed groups, 70% of females exposed to 5 and 15 mg/kg bw/d, and 65% of those exposed to 25 mg/kg bw/d had a regular estrous cyclicity. Despite this tendency to decrease, no statistically significant effect of the treatment was found.

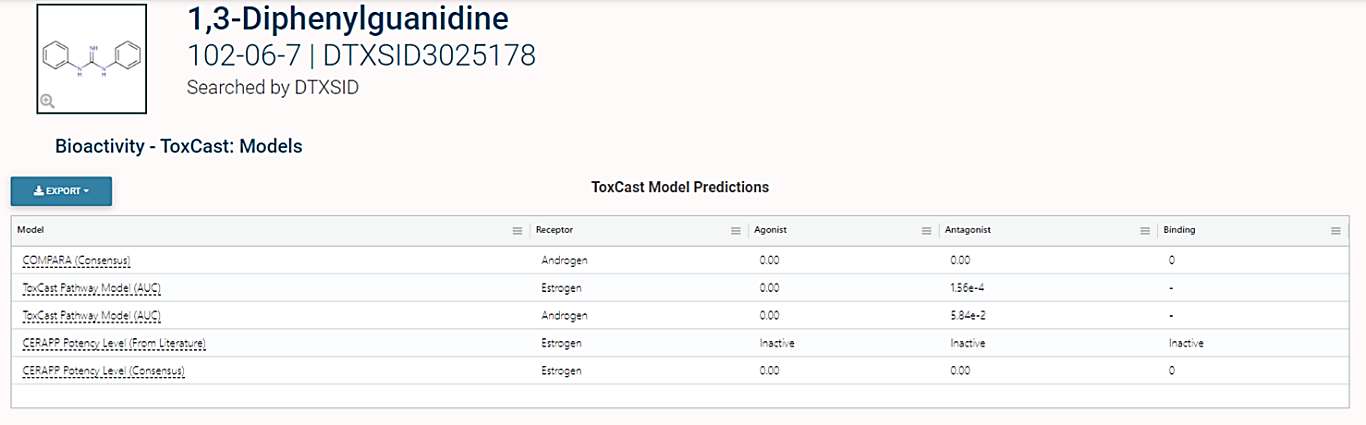
A literature review on Pubmed was performed using the keywords “1-3 diphenylamine OR DPG”, and did not allow to retrieve additional relevant data regarding potential ED adverse effects. The database relevant to fertility and development was already considered when assessing toxicity for the reproduction in the scope of the CLH report for the substance and no additional information was considered relevant for endocrine disruption assessment.

Endocrine activity

Kreider & Panko (2016), published a document in which DPG underwent testing for endocrine disruption potential using the Tier 1 screening assays developed for the U.S. EPA’s EDSP (U.S. EPA, 2011, 2015). On the basis of these tests, the weight of evidence (WoE) analysis indicates that DPG is unlikely to act as an endocrine disruptor through EATS modes of action. This information was complemented with a literature review of the potential mode of action of DPG, ToxCast data, Danish QSAR data and OECD QSAR Toolbox data on DPG.

In ToxCast ER agonist and antagonist models, as well as in the AR agonist model, with area under the curve (AUC) values of 0.00 or 0.000156, DPG is considered inactive. With an AUC value of 0.0584, the AR antagonist model is inconclusive; AR antagonist assays in the ToxCast database were thus further investigated.

**Table 17: ToxCast Model Prediction (data extracted in December, 2022)**



|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Model | Receptor | Agonist | Antagonist | Binding |
| COMPARA (Consensus) | Androgen | 0 | 0 | 0 |
| ToxCast Pathway Model (AUC)\* | Estrogen | 0 | 0,000156 | - |
| ToxCast Pathway Model (AUC)\* | **Androgen** | 0 | **0,0584** | - |
| CERAPP Potency Level (From Literature) | Estrogen | Inactive | Inactive | Inactive |
| CERAPP Potency Level (Consensus) | Estrogen | 0 | 0 | 0 |

<https://comptox.epa.gov/dashboard/chemical/bioactivity-toxcast-models/DTXSID3025178>

\*The ToxCast Pathway Model (AUC) provides a value (range from 0-1) for Androgen and Estrogen receptor activity, each (in agonist or antagonist mode). If any of these values exceed 0.1, then there is a significant interaction.

DPG was active in 4 of these AR assays. However, in the ACEA\_AR\_antagonist\_80hr test, the LogAC50 value is similar to the one in the corresponding viability assay. DPG was active in TOX21\_AR\_LUC\_MDAKB2\_Antagonist\_0.5nM\_R1881 and TOX21\_AR\_LUC\_MDAKB2\_Antagonist\_10nM\_R1881, although at a lower concentration in presence of 10 nM R1881 (LogAC50=0.52) than with 0.5 nM R1881 (LogAC50=0.89). No diminution of the cell viability was observed in the corresponding tests. Based on ToxCast assays, no clear AR antagonist activity was thus evidenced. In a binding test to AR (OT\_AR\_ARSRC1\_0960), the substance is active at a value of LogAC50=1.36. As post-implantation losses, increased duration of gestation and dystocia have been sometime associated with aromatase inhibition[[19]](#footnote-20), the steroidogenesis endpoint was also investigated in the ToxCast database. DPG was active in the aromatase inhibition test (TOX21\_Aromatase\_Inhibition) but with a LogAC50 value similar to the one in the corresponding viability assay. Moreover, there was no decrease in the synthesis of estradiol or estrone in the H295R cellular assay (CEETOX\_H295R\_ESTRADIOL\_noMTC\_dn:INACTIVE and CEETOX\_H295R\_ESTRONE\_noMTC\_dn:INACTIVE). In this assay, the only reported effects (without effects on the cellular viability) are related to decreased synthesis of desoxycorticosterone (LogAC 50: 1.7), cortisol (LogAC50: 1.66) and corticosterone (LogAC50: 1.53) (as well as Desoxycortisol, Androstenedione and OHpregnenolone, with an effect above baseline only at the highest concentration). Based on these data, the only possible endocrine activity of DPG seems therefore to be on the corticosteroid pathway.

In the EOGRTS study on rats (unpublished study report, 2021), an increase in adrenal gland weight was observed although it is not supported with histological alteration, and hormone measurement were not available. Moreover, it was impossible to discriminate which of the medulla or cortical part are involved in the increase in the adrenal gland weight preventing to link the adverse effect to a possible endocrine mode of action. Thus, a plausible link between the effect and the endocrine activity is not possible and this endpoint was not further investigated.

**Table 18: ToxCast Data (data extracted in December, 2022)**

|  |  |  |  |
| --- | --- | --- | --- |
| **Intended target** | **Assay family** | **Name** | **Result** |
| **AR** | Agonist activity | ACEA\_AR\_agonist\_80hr | INACTIVE |
| UPITT\_HCI\_U2OS\_AR\_TIF2\_Nucleoli\_Agonist | INACTIVE |
| TOX21\_AR\_BLA\_Agonist\_ratio | INACTIVE |
| TOX21\_AR\_LUC\_MDAKB2\_Agonist | INACTIVE |
| TOX21\_AR\_LUC\_MDAKB2\_Agonist\_3uM\_Nilutamide | INACTIVE |
| OT\_AR\_ARELUC\_AG\_1440 | INACTIVE |
| ATG\_AR\_TRANS\_up | INACTIVE |
| Antagonist activity | ACEA\_AR\_antagonist\_80hr (22Rv1 cell proliferation measured by impedence) | LogAC50 = 1 |
| TOX21\_AR\_LUC\_MDAKB2\_Antagonist\_0.5nM\_R1881 | LogAC50 = 0.89 |
| TOX21\_AR\_LUC\_MDAKB2\_Antagonist\_10nM\_R1881 | LogAC50 = 0.52 |
| TOX21\_AR\_BLA\_Antagonist\_ratio | INACTIVE |
| UPITT\_HCI\_U2OS\_AR\_TIF2\_Nucleoli\_Antagonist | INACTIVE |
| ATG\_AR\_TRANS\_dn | INACTIVE |
| Binding | OT\_AR\_ARSRC1\_0960 | LogAC50 = 1.36 |
| OT\_AR\_ARSRC1\_0480 | INACTIVE |
| Viability | ACEA\_AR\_antagonist\_AUC\_viability | LogAC50 = 1.04 |
| TOX21\_AR\_BLA\_Antagonist\_viability | INACTIVE |
| TOX21\_AR\_LUC\_MDAKB2\_Antagonist\_0.5nM\_R1881\_viability | INACTIVE |
| TOX21\_AR\_LUC\_MDAKB2\_Antagonist\_10nM\_R1881\_viability | INACTIVE |
| **Thyroid** | Thyroid hormone receptor (ThR) | ATG\_THRa1\_TRANS\_dn | INACTIVE |
| ATG\_THRa1\_TRANS\_up | INACTIVE |
| TOX21\_TR\_LUC\_GH3\_Agonist | INACTIVE |
| TOX21\_TR\_LUC\_GH3\_Antagonist | INACTIVE |
| TSH Receptor (TSHR) | TOX21\_TSHR\_HTRF\_Agonist\_ratio | INACTIVE |
| TOX21\_TSHR\_HTRF\_Antagonist\_ratio | INACTIVE |
| TOX21\_TSHR\_HTRF\_wt\_ratio | INACTIVE |
| TRH receptor (TRHR) | TOX21\_TRHR\_HEK293\_Agonist | LogAC50 = 1.03 |
| TOX21\_TRHR\_HEK293\_Antagonist | LogAC50 = 1.29 |
| thyroid hormone responsive (THSRP) | LTEA\_HepaRG\_THSRP\_dn | LogAC50 = 1.24 |
| LTEA\_HepaRG\_THSRP\_up | INACTIVE |
| **S** | Aromatase inhibition | TOX21\_Aromatase\_Inhibition | LogAC50 = 1.45 |
| Viability | TOX21\_Aromatase\_Inhibition\_viability | LogAC50 = 1.36 |
| Synthesis | CEETOX\_H295R\_11DCORT\_noMTC\_dn | LogAC50 = 1.84 |
| CEETOX\_H295R\_ANDR\_noMTC\_dn | LogAC50 = 1.95 |
| CEETOX\_H295R\_CORTIC\_noMTC\_dn | LogAC50 = 1.53 |
| CEETOX\_H295R\_CORTISOL\_noMTC\_dn | LogAC50 = 1.66 |
| CEETOX\_H295R\_DOC\_noMTC\_dn | LogAC50 = 1.70 |
| CEETOX\_H295R\_OHPREG\_noMTC\_dn | LogAC50 = 1.92 |
| CEETOX\_H295R\_11DCORT\_noMTC\_up | INACTIVE |
| CEETOX\_H295R\_ANDR\_noMTC\_up | INACTIVE |
| CEETOX\_H295R\_CORTIC\_noMTC\_up | INACTIVE |
| CEETOX\_H295R\_CORTISOL\_noMTC\_up | INACTIVE |
| CEETOX\_H295R\_DOC\_noMTC\_up | INACTIVE |
| CEETOX\_H295R\_ESTRADIOL\_noMTC\_dn | INACTIVE |
| CEETOX\_H295R\_ESTRADIOL\_noMTC\_up | INACTIVE |
| CEETOX\_H295R\_ESTRONE\_noMTC\_dn | INACTIVE |
| CEETOX\_H295R\_ESTRONE\_noMTC\_up | INACTIVE |
| CEETOX\_H295R\_OHPREG\_noMTC\_up | INACTIVE |
| CEETOX\_H295R\_OHPROG\_noMTC\_dn | INACTIVE |
| CEETOX\_H295R\_OHPROG\_noMTC\_up | INACTIVE |
| CEETOX\_H295R\_PROG\_noMTC\_dn | INACTIVE |
| CEETOX\_H295R\_PROG\_noMTC\_up | INACTIVE |
| CEETOX\_H295R\_TESTO\_noMTC\_dn | INACTIVE |
| CEETOX\_H295R\_TESTO\_noMTC\_up | INACTIVE |
| CEETOX\_H295R\_MTT\_cell\_viability\_dn | INACTIVE |
| CEETOX\_H295R\_MTT\_cell\_viability\_up | INACTIVE |

Based on ToxCast assays, the results from TOX21\_TRHR\_HEK293\_Agonist (LogAC50 = 1.03), TOX21\_TRHR\_HEK293\_Antagonist (LogAC50 = 1.29) and LTEA\_HepaRG\_THSRP\_dn (LogAC50 = 1.24) does not allow to report an evidence for a clear T activity. A potential for TPO inhibition was identified *in vitro* by the Danish QSAR Database. As mentioned above, effects on T4 and TSH were observed in the EOGRTS study. A statistically significant increase of T4 concentrations (+38% versus the controls) was noticed at 25 mg/kg bw/d in P generation females. It was associated with a tendency to decrease in TSH concentrations (-10% not statistically significant). A statistically significant decrease of T4 concentrations was observed in males of F1 generation (cohort 1A) at 5 and 15 mg/kg bw/d. However, no histopathological change was observed in the thyroid gland.

**Table 19: Danish QSAR data on DPG (data extracted in December, 2022)**

| Models | Battery | CASE Ultra | Leadscope | SciQSAR |
| --- | --- | --- | --- | --- |
| Estrogen Receptor α Binding, Full training set (Human *in vitro*) | NEG\_IN | NEG\_IN | NEG\_IN | NEG\_IN |
| Estrogen Receptor α Binding, Balanced Training Set (Human *in vitro*) | NEG\_IN | NEG\_IN | NEG\_OUT | NEG\_IN |
| Estrogen Receptor α Activation (Human *in vitro*) | NEG\_OUT | NEG\_IN | NEG\_OUT | INC\_OUT |
| Estrogen Receptor Activation, CERAPP data (*in vitro*) | N/A | N/A | NEG\_IN | N/A |
| Androgen Receptor Inhibition (Human *in vitro*) | NEG\_IN | NEG\_IN | NEG\_OUT | NEG\_IN |
| Androgen Receptor Binding, CoMPARA data (*in vitro*) | N/A | N/A | NEG\_IN | N/A |
| Androgen Receptor Inhibition, CoMPARA data (*in vitro*) | N/A | N/A | NEG\_IN | N/A |
| Androgen Receptor Activation, CoMPARA data (*in vitro*) | N/A | N/A | NEG\_IN | N/A |
| **Thyroperoxidase (TPO) inhibition QSAR1 (Rat *in vitro*)** | N/A | N/A | **POS\_IN** | N/A |
| **Thyroperoxidase (TPO) inhibition QSAR2 (Rat *in vitro*)** | N/A | N/A | **POS\_IN** | N/A |
| Sodium/iodide symporter (NIS), higher sensitivity | N/A | N/A | INC\_OUT | N/A |
| Sodium/iodide symporter (NIS), higher specificity | N/A | N/A | NEG\_OUT | N/A |
| Thyroid Receptor α Binding (Human *in vitro*) |  |  |  |  |
| * mg/L |  | 33793.86 | 1741.678 | 16.22699 |
| * µM |  | 159955.8 | 8243.85 | 76.80687 |
| * Positive for IC50 ≤ 10 µM |  |  |  |  |
| * Positive for IC50 ≤ 100 µM |  |  |  |  |
| * Domain | OUT | OUT | OUT | OUT |
| Thyroid Receptor β Binding (Human in vitro) |  |  |  |  |
| * mg/L |  | 6836.567 | 16.25653 | 57.66839 |
| * µM |  | 32359.38 | 76.94672 | 272.9606 |
| * Positive for IC50 ≤ 10 µM |  |  |  |  |
| * Positive for IC50 ≤ 100 µM |  |  |  |  |
| * Domain | OUT | OUT | OUT | OUT |
| Arylhydrocarbon (AhR) Activation – Rational final model (Human *in vitro*) | N/A | N/A | INC\_OUT | N/A |
| Arylhydrocarbon (AhR) Activation – Random final model (Human *in vitro*) | N/A | N/A | POS\_OUT | N/A |
| Pregnane X Receptor (PXR) Binding (Human *in vitro*) | NEG\_IN | NEG\_IN | NEG\_IN | NEG\_IN |
| Pregnane X Receptor (PXR) Binding (Human *in vitro*) NEW | N/A | N/A | NEG\_IN | N/A |
| Pregnane X Receptor (PXR) Activation (Human *in vitro*) | N/A | N/A | NEG\_IN | N/A |
| Pregnane X Receptor (PXR) Activation (Rat *in vitro*) | N/A | N/A | NEG\_IN | N/A |
| CYP3A4 Induction (Human *in vitro*) | N/A | N/A | NEG\_IN | N/A |
| Constitutive Androstane Receptor (CAR) Activation at max. 20 µM (*in vitro*) | N/A | N/A | NEG\_IN | N/A |
| Constitutive Androstane Receptor (CAR) Activation at max. 50 µM (*in vitro*) | N/A | N/A | NEG\_IN | N/A |
| Constitutive Androstane Receptor (CAR) Inhibition at max. 20 µM (*in vitro*) | N/A | N/A | INC\_OUT | N/A |
| Constitutive Androstane Receptor (CAR) Inhibition at max. 50 µM (*in vitro*) | N/A | N/A | NEG\_OUT | N/A |
| INC: inconclusive. A definite call within the defined applicability domain could not be made.  NEG: negative  POS: positive  IN: inside applicability domain  OUT: outside applicability domain  N/A: Not applicable | | | | |

In conclusion, additional OECD level 1 and 2 data as summarized in the tables above did not bring other relevant information pointing toward an endocrine activity. Although reprotoxic adverse effects were noted for the substance DPG, it is not possible on the basis of the available data to establish an endocrine mode of action corresponding to the adverse effects.

Thus, there are no sufficient indications to consider that the substance has ED properties and the ED assessment of DPG will not be further investigated for the moment by the aMSCA.

### Reprotoxicity EOGRTS OECD TG 443 study: summary

**Table 20: Summary table of EOGRTS**

| **Method, guideline, deviations if any, species, strain, sex, no/group** | **Test substance, dose levels duration of exposure** | **Results** | **Reference** |
| --- | --- | --- | --- |
| Gavage  OECD TG 443  Extended one-generation reproductive toxicity (Cohorts 1A, and 1B with extension to cohort F2)  GLP  Rats, Sprague-Dawley  Males and  females  Number of animals per sex per dose:  -Parental generation : 24 per sex per dose  - F1: 20 per sex per dose (Cohorts 1A and 1B)  Reliability 1  Key study | 1,3-diphenylguanidine  Purity: 98.7%  Vehicle: 0.5% methylcellulose in drinking water treated by reverse osmosis  Dose levels: 5, 15, 25 mg/kg bw/d  Administration: once daily  Duration of exposure:  -P males: at least 10 weeks of treatment  -P females: at least 8 to 10 weeks of treatment  -Cohort 1A: both males and females: from weaning (PND 22) until euthanasia (from PND 90 to PND 93 maximum).  -Cohort 1B: In males: from weaning (PND 22.) for at least 10 weeks before mating, during the mating period (up to 2 weeks), and after euthanasia of F2 pups (on PND 4). In females: from weaning (PND 22.) for at least 10 weeks before mating, during the mating period (up to 2 weeks), during gestation, during lactation until PND 4 inclusive until euthanasia for females with no delivery (26 days after the last day of the mating period).  Historical control data indicated in the study report were considered as concomitant studies as they are based on only two studies for P generation and F1 pups and on only one study for an extension to a F2 generation. | **General toxicity :**  **Body weight and body weight gain :**  P generation: no adverse effect during the premating, mating, gestation or lactation periods.  Lactating F1 pups: in males and females, at 25 mg/kg bw/d, body weight lower at PND1 (Males: 7.7g vs 8.4g for controls and females: 7.3g vs 7.8g for controls). Statistically significant in males. Body weights return to control values thereafter.  Cohort 1A: no adverse effect on body weight and body weight change.  Cohort 1B: no adverse effect on body weight and body weight change during premating, post-mating and pregnancy period and lactation period.  Lactating F2 pups: in both sexes, body weight lower at PND1 (Males: 7.3g vs 8.1g for controls and females: 7.2g vs 7.7g in controls). Statistically significant in males. At PND4, there is a tendency toward a return to control values and differences were not statistically significant.  **Food consumption :**  No adverse effect seen in P Generation, cohort 1A and cohort 1B during the study.  **Neurotoxicity :**  In P Generation, at 25 mg/kg bw/d, at the end of the pregnancy period (from Study Day 42), series of clinical signs suggestive of neurologic disorders seen in 8 out of 18 surviving females (e.g. clonic convulsion, locomotor difficulties, loss of balance, staggering gait and/or tonic seizures). Disorders transient and observed after dosing only.  In cohort 1B, at 25 mg/kg bw/d, in both sexes, series of clinical signs suggestive of neurologic disorders also observed (e.g. clonic/tonic convulsion, loss of balance and/or staggering gait) mainly from Study Day 94 after dosing for 1 to 3 days.  **Immunology findings :**  Cohort 1A : in males at 15 mg/kg/d, when compared with controls, statistically significant increase of NK cells both in terms of relative (4.8 vs. 3.4%) and absolute cells counts (11397 cells/mg of spleen compared to 7001 cells/mg of spleen) and a decrease of T cells in terms of relative counts (36.6 vs. 42.5%). No significant difference was observed at 25 mg/kg bw/d.  In females, at 25 mg/kg bw/d, when compared with controls, statistically significant decrease of NK cells, both in terms of relative (2.6 vs. 3.8% of splenocytes) and absolute counts (5879 vs. 10713 cells/mg of spleen).  **Organs observations :**  P generation :  From 15 mg/kg bw/d:  Statistically significant increase in liver weights in males, correlated with the microscopic hepatocellular hypertrophy. Same trend with lower amplitude seen in females without significance.  Statistically significant increased absolute and relative-to-body adrenal gland weights in females (up to +23%). No microscopic correlates.  Cohort 1A: statistically significant increased absolute and relative-to-body liver weights in females treated at ≥ 5 mg/kg/d and in relative-to-body weights in males treated at 25 mg/kg bw/d, correlated with hepatocellular hypertrophy at microscopic examination  Cohort 1B: increased absolute (statistically significant at 15mg/kg bw/d) and/or relative-to-body liver weights (statistically significant from 15mg/kg bw/d in males) recorded in males and females treated at ≥ 15 mg/kg/d.  Other findings :  At 5 mg/kg bw/d, in P generation, one female with an adenocarcinoma in mammary gland.  At 25 mg/kg bw/d, in cohort 1B generation, one female with an adenocarcinoma in mammary gland.  **Effects on fertility and sexual function :**  **Estrous cycle:**  In P generation, tendency toward a lower mean number of day of metestrus from 5mg/kg bw/d (4.9 for controls, 4.0 at 5 mg/kg/day, 3.7 at 15 mg/kg/day and 3.3 at 25 mg/kg bw/d). Statistical significance achieved at 15 and 25 mg/kg bw/d  Tendency toward an increase in the mean number of estrus (3.5 for controls, 3.8 at 5 mg/kg bw/d, 3.4 at 15 mg/kg bw/d and 4.3 at 25 mg/kg bw/d). Statistical significance at 25 mg/kg bw/d.  Same trends observed in cohort 1A at 25 mg/kg/d without statistical significance (metestrus: **3.8 vs** 4.6 in controls and 3.0-3.5 in concomitant studies estrus: 4.3 vs 4.0 in controls and 3.7-3.8 in concomitant studies).  **Duration of gestation :**  In P generation, trend toward increased period of gestation on an individual basis. At 5 mg/kg bw/d, 2/22 females with a gestation period of 24 days associated with a high pup mortality rate. **At 25 mg/kg bw/d, increased number of females with 23-day gestation periods** (7/24) (not statistically significant) when compared to the control group associated to a high post-implantation loss. No difference in mean duration of gestation.  In the Cohort 1B, same trend observed. At 15 mg/kg bw/d 1/18 female at 25 mg/kg bw/d 7/19 females had 23 days of gestation. Statistically significant increase of the mean duration of gestation at 25 mg/kg bw/d (22.3 vs 21.9 in controls).  **Reproduction difficulties:**  In P generation, from 5 mg/kg bw/d, presence of females presenting **reproduction difficulties:** red vaginal discharge and difficulty to deliver and dystocia.  At 5 mg/kg bw/d: one female presented reddish vaginal discharge and dead litter. At 15 mg/kg bw/d, one female presented dead litter and one female had dystocia with abdomen increased in size. At 25 mg/kg bw/d, 3 females presented dead litters and one female presented difficulty to deliver.  In cohort 1B, from 15 mg/kg/d, presence of females presenting reproduction difficulties: two females treated at 15 mg/kg bw/d had dead litter and at 25 mg/kg bw/d two females had dead litters and one female presented dystocia.  Follicles count:  Cohort 1A : Tendency toward a dose-related decrease of the mean number of primordial follicles (8.68 at 5 mg/kg bw/d, 6.65 at 15 mg/kg bw/d, 5.75 at 25 mg/kg bw/d vs 9.31 mg/kg/d in controls) (no statistical significance achieved).  **Effects on development:**  **Post-implantations loss:**  In P generation, at 25 mg/kg bw/d, statistically significant increase of the mean percent of post-implantation loss (27.1% vs 15.6% in controls).  In cohort 1B, non-statistically significant dose-related increase of the mean percent of post-implantation loss (18.6% at 5mg/kg bw/d, 22.1% at 15mg/kg bw/d, 24.6% at 25 mg/kg bw/d vs 13.6% in controls).  **Pups survival:**  F1 pups:  At PND 1, from 5 mg/kg bw/d, dose-related tendency towards lower number of viable F1 pups (down to 9.3 vs. 12.0 live pups at 25 mg/kg bw/d) and live birth index (down to 72.8 vs. 95.1% at 25 mg/kg bw/d) when compared with controls (not statistically significant). From 5 mg/kg bw/d, during lactation, dose-related statistically significant increase of the mortality of F1 pups between PND 1 to 4 (14 pups (4.9%) for controls, 35 pups (12.5%) at 5 mg/kg bw/d, 47 pups (16.2%) at 15 mg/kg bw/d, 82 (32.3%) at 25 mg/kg bw/d.  Number of litter affected statistically significant at 25 mg/kg bw/d.  Trend toward a decreased F1 pups viability index before culling, on PND 4 (not statistically significant) (94.8% for controls, 90.1% at 5 mg/kg bw/d, 85.0% at 15 mg/kg bw/d, 74.4% at 25 mg/kg bw/d and 98.0% for concomitant studies)  From 5 mg/kg bw/d, presence of clinical signs in F1 found dead pups (cold to the touch, absence of milk in the stomach, dehydration, emaciated appearance, pallor) (no statistical significance).  F2 pups :  At 25 mg/kg bw/d, statistically significant decrease in the mean number of live F2 pups at PND 1 compared to controls and in a concomitant study (7.8 vs 11.4 in controls) and decrease of the live birth index from 15 mg/kg bw/d (not statistically significant) compared to controls (84.1% at 15 mg/kg bw/d, 67.5% at 25 mg/kg bw/d vs 100%).  From 15 mg/kg bw/d, dose-related statistically significant increase of mortality of F2 pups between PDN 1 and 4(2 pups (1.0%) for controls, 56 pups (24.2%) at 15 mg/kg bw/d, 73 (37.4%) at 25 mg/kg bw/d. Tendency toward a decreased viability index F2 pups on PND4 (not statistically significant) (99.0% for controls, 97.4% at 5 mg/kg bw/d, 80.6% at 15 mg/kg bw/d, 56.6% at 25 mg/kg bw/d).  From 15 mg/kg bw/d, dose-related increase of F2 pups with findings on PND1: cold to the touch from 15 mg/kg bw/d and/or with emaciated appearance and hypoactivity at 25 mg/kg bw/d (no statistical significance).  From 5 mg/kg bw/d, dose-related increased number of pups found dead due to autolysis (7 pups, one litter at 5mg/kg bw/d. 27 pups, 10 litters at 15 mg/kg bw/d, 22 pups, 11 litters at 25 mg/kg bw/d) (no statistical significance).  From 15 mg/kg bw/d, increase of pups with an absence of milk in the stomach (8 pups, 4 litters at 15 mg/kg bw/d, 23 pups, 8 litters at 25 mg/kg bw/d) (no statistical significance). | Unpublished study report, 2021 |

# Exposure assessment

The exposure assessment was realised in the registration dossiers for industrial and professional workers, for consumers and for the environment. The exposure scenarios covers different lifestage of the substance 1,3-diphenylguanidine (DPG): manufacturing of DPG, formulation and re-packaging, manufacturing of articles (tyres and general rubber goods), use of tyres by consumers and garage owners, storage of used tyres before recycling, tyres recycling (End of Life Tyres, ELT), re-use of ELT and use of General Rubber Goods (GRG) articles.

The tonnage values used in the exposure assessment were obtained following a survey done in 2015 (tonnage average on 2012, 2013 and 2014). Only 2 registrants (and manufacturers) of DPG are in EU.

## Human health

### Exposure scenario for workers and consumers covered in the registration dossiers

In the context of this RMOA, only the latest version of the CSR that have been revised further to the recent EOGRTS (2021) study were analysed.

The exposure scenarios are detailed in the confidential annex.

### Exposure to DPG reported in literature

**Presence of DPG in gloves and shoes**

Contact allergy to DPG is largely reported in the literature (Hansen *et al*. 2021). The main type of reactions and population identified are sensitization reactions to rubber gloves in healthcare workers. Indeed, the presence of DPG is reported in rubber gloves (Dejonckheere *et al*. 2019, Hamnerius *et al*. 2014, Crepy 2016). These studies were conducted in different countries worldwide. Several other studies report foot dermatitis due to the presence of DPG in shoes (Traidl *et al*. 2021, Suhail *et al*. 2009, Saha *et al*. 1993, Ross 1969).

Corazza *et al*. (2021) also reported the presence of DPG in boxing gloves.

A harmonized classification as Skin Sens. 1A, H317 is proposed by aMSCA.

**Presence of DPG in drinking water**

Several recent publications indicate the presence of DPG in drinking water sources, drinking water treatment plants and drinking water.

Zhang *et al*. (2023) studied the presence of tire additives in drinking water treatment plant. The presence of DPG and 1,3-diphenylurea, a transformation product of DPG, were reported. In the source samples of drinking water, the authors indicated that the concentration of detected accelerators (which included DPG and 1,3-diphenylurea) ranged from 35.5 ng/L to 183 ng/L. In the DWTP samples, concentrations of detected compounds (which included DPG and 1,3-diphenylurea) ranged from tens to hundreds of nanograms per liter.

Ichihara *et al*. (2023) analyzed the presence of guanidine derivatives in different type of water in Japan. DPG was detected in tap water with frequency of detection of 100% from 2 samples (concentration not specified).

Gollong *et al*. (2022), analyzed the presence of chemicals in a drinking water production and wastewater treatment plant in Germany. DPG was detected at a median concentration of 4 ng/L (probably a median of the concentration of DPG in all types of water tested in the study, not only drinking water).

One of the possible source of DPG emission may be the migration from water pipe designed to transport treated drinking water. Tang *et al*. (2015) investigated the presence and distribution of selected semi-volatile organic compounds from source water to tap water in Changsha, China. The potential migration of specific compounds from pipe material into water at different periods of pipeline life was studied. DPG was found to be migrating from high density polyethylene (HDPE) pipe material. DPG was found in drinking water at different sampling sites at concentrations up to 0.56 mg/L (0.23-0.47 mg/L in the residential district).

Diera *et al*. (2023) studied the migration of compounds from high-density polyethylene pipes in a drinking water distribution system in Denmark. Among them DPG was detected in the water. The proposed origin was polyethylene (PE) and rubber seals. Five rubber seals from different valves commonly used in the water distribution system, consisting of EPDM (Ethylene Propylene Diene Monomer Rubber) and NBR (Nitrile Butadiene Rubber) rubber were investigated. DPG was found in EPDM rubber gasket plate, which is used to make custom gaskets in waterworks. DPG is included in the positive list (Combined List – lists of substances under review) of the 4MSI Common Approach on Organic Materials in Contact with Drinking Water[[20]](#footnote-21). The NL authority member state indicate a Maximum Tolerable Concentration (MTC) of 0.0025 mg/L for the use of this substance as rubber in contact with drinking water.

DPG was also detected in drinking water sources in Germany (Neuwald *et al*. 2022) at a median concentration of 0.17 ng/L with a frequency of detection of 17%. The authors also studied the emission pattern of 34 substances by using a correlation analysis to investigate patterns of co-occurrence. DPG did not correlate well with the other compounds tested and the authors concluded that DPG emission into drinking water sources is likely related to leachate from road run-off during rain events and that consequently DPG concentrations may be more dependent on the sampling time than on the sampling location.

**Presence of DPG in indoor dust**

The presence of DPG was reported in indoor dust.

Tan *et al*. (2021) studied the presence of synthetic antioxidants in house dust from different locations in the Asia-Pacific Region and the United States. Among them, DPG was detected with a median concentration of 5030−11 400 ng/g in house dust from the studied regions except for Hanoi (305 ng/g).

Li & Kannan (2023) studied the occurrence of DPG in indoor dust from 11 countries. DPG was found in 100% of the house dust samples, at median concentrations of 140 ng/g (range: 2.1 – 11 000 ng/g). Elevated concentrations of DPG were found in dust from certain microenvironments (e.g., offices and cars). The authors assessed human exposure to DPG through dust ingestion and the following ranges were 0.07−4.40, 0.09−5.20, 0.03−1.70, 0.02−1.04, and 0.01−0.87 ng/kg bw/day for infants, toddlers, children, teenagers, and adults, respectively.

Shin *et al*. (2020) measured the concentrations of consumer product chemicals in California house dust. The median concentration of DPG was 3218 ng/g of dust and was detected in all dust samples.

**Presence of DPG in air**

Johannessen *et al*. (2022) studied the airborne concentrations of chemicals associated with tire-wear in megacities using passive samplers. DPG was detected in every studied megacity above limits of quantification at estimated concentrations between 45.0 to 199 pg/m3 (mean = 93.9 pg/m3). DPG was detected in the highest estimated concentration out of any analyte included in this study.

**Other contamination with DPG**

Lin *et al*. (2007) detected a contaminant during the content uniformity test of a drug product (tablet formulation) and concluded that it was most likely DPG. They proposed as the potential source of DPG as coming from the safety filler of the pipette bulb used to prepare the sample solutions during the drug analysis.

Zidan *et al*. (2017) also detected the presence of DPG in a pharmaceutical product (oxytocin). DPG was coming from rubber closures used in pre-filled syringes. DPG was able to interact with oxytocin.

**Conclusion on human health exposure:**

Overall, data from the registration dossiers and literature indicate human exposure of DPG is coming from multiple sources and seems to be continued.

In the literature, more consumer’s uses are reported: shoes, rubber gloves, socks. Exposure can also come from drinking water or dusts ingestion or inhalation of DPG present in the air. Two publications exposed the contamination of drugs due to migration of DPG from the equipment used to handle the drug.

This leads to uncertainties about the representativeness of the human health exposure scenarios presented in the registration dossiers for consumers. There are also uncertainties on the residual amount of DPG present in the articles. No data was found in the literature.

## Environment

### Introduction to the assessment for the environment

The exposure scenarios are detailed in the confidential annex.

### PNEC derivation

**Table 23: PNEC derivation** **used in the environmental risk assessment**

| **PNECs derivation used in the environmental risk assessment** | | |
| --- | --- | --- |
| Environmental compartment | Hazard conclusion | Remarks/Justification |
| Freshwater | PNEC aqua (freshwater) = 30 µg/L | Data from substance evaluation conclusion document (ANSES, 2020). No new data were provided and the data are in line with the Registrants dossier. |
| Marine water | PNEC aqua (marine water) = 3 µg/L |
| Intermittent releases to water | PNEC aqua (intermittent releases) = 14 µg/L |
| Sediment (freshwater) | PNEC sediment (freshwater) = 2.51 mg/kg sediment dw |
| Sediment (marine water) | PNEC sediment (marine water) = 0.251 mg/kg sediment dw |
| Sewage Treatment Plant | PNEC STP = 1.47 mg/L |
| Soil | PNEC soil = 0.404 mg/kg soil dw-1 |
| Air | No hazard identified |
| Secondary poisoning | No potential for bioaccumulation |

### Fate and distribution parameters

The following substance properties are used in the fate estimation as recommended by the Guidance on information requirements and chemical safety assessment, chapter R.16 and as concluded in ANSES (2020).

**Table 24: Physical-chemical, environmental fate data used in the environmental risk assessment**

| **Physical-chemical, environmental fate data used in the environmental risk assessment** | | |
| --- | --- | --- |
| **Input** | **Value** | **Unit** |
| Molecular weight | 211 | g.mol-1 |
| Water solubility | 325mg/L at pH 10.32 | mg.l-1 [20 °C] |
| Vapour pressure | 3.7E-10 | Pa [25°C] |
| Henry constant | 1.07E-10 | Pa.m-3.mol-1[12°C] |
| Octanol-water partition coefficient | 2.42 | [log10] |
| Koc | 807 | l.kg-1 [20 °C] |  |
| Biodegradability | Based on OECD TG 301D :  readily biodegradable  fulfilling the 10-day window criteria | [-] |
| DT50 in surface water | Based on OECD TG 111: hydrolytically stable  Based on equivalent to OECD TG 309:  % Degradation of test substance (test mat. analysis):  3 after 3d  78 after 7d  100 after 14d | d [21-25°C] |
| DT50 in soil | 30 | Default value |

|  |  |
| --- | --- |
| **Calculated fate and distribution in the STP – SimpleTreat v4.0** | |
| **Compartment** | **Percentage [%]** |
| Air | 4.79E-09 |
| Water | 7.54 |
| Sludge | 6.82 |
| Degraded in STP | 85.64 |

### Combined exposure assessment

The aMSCA did not recalculated the regional PEC. The regional predicted environmental concentrations as reported by the Registrants are available in the confidential annex.

### Monitoring data from literature

Monitoring data were obtained from Norman database[[21]](#footnote-22). All data come from a campaign conducted from June to August 2019 in the Danube river basin (Germany, Austria, Croatia, Serbia, Romania, Slovakia, Hungary, Bulgaria and Czech Republic). Only 7 measurements were available for groundwater and DPG was not found in these samples (LOD and LOQ = 0.005 µg/L). In surface water, more than 100 samples were analysed and the concentration of DPG was up to 0.167 µg/L. In WWTP, around 20 samples were analysed and DPG was found in all samples at level 0.038-0.766 µg/L.

These values are lower than the PNEC for surface water (30 µg/L). However, these samples might not be fully representative of the environmental situation as they were obtained in only one campaign of 3 months in 2019, and come from a single hydro-geological region of Eastern Europe.

A review of the scientific literature was also conducted to characterise the occurrence of DPG in the aquatic compartment.

In Western Japan (Ichihara, 2023), DPG was detected in all the samples in lake water, river water, sewage effluent, and tap water at level up to 44 ng/L.

In another study, DPG was detected in all 14 analyzed water samples (surface water, groundwater, bank filtrate, as well as a plant for drinking water production) from Germany, Spain and The Netherlands, at higher estimated concentrations up to 100 ng/L (Schulze et al., 2019).

The range, mean, median concentrations, and detection frequency of DPG was also measured in surface water of Zhujiang and Dongjiang rivers, in China. DPG was detected at a frequency of 100 %. The concentration range was 3.47-1894 ng/L and the study reported that the concentrations were generally higher during the dry season, probably due to a more limited dilution. The DPG concentrations in rivers have been reported to be 13–1079 ng/L in Australia (Rauert et al., 2022), 5–540 ng/L in USA (Hou et al., 2019), and 220 ng/L in Canada (Johannessen et al., 2022).

In surface runoff, the DPG concentration reached 58.8 μg/L in a study conducted in China (Zhang, 2023). In a Canadian study (Challis *et al*. 2021), semi-quantification of DPG revealed that this substance was the most abundant among 5 target coumpounds, with average concentrations of 60 μg/L in stormwater urban runoff. The maximum observed concentrations of DPG were up to 364 μg/L.

Abrasion particles of tyres are emitted to the environment and research has shown that tyre additives like DPG can enter the environment through the leaching of automobile tyre wear particles. Under the volatilization, leaching, and transformation action on tyres particles by sunlight and rain, tyre additives are released into urban water systems, such as surface rainfall runoff, wastewater treatment plants, receiving surface waters, and drinking water treatment plant (Zhang *et al*. 2023). As reported in Sieber *et al*. (2020), the estimated *per capita* flows of rubber was in year 2018 in Switzerland, 1.29 ± 0.45 kg/capita of rubber emitted from tyre wear (97%) and rubber granules (3%). Street cleaning and waste water treatment removed around 26% of this rubber mass before finally reaching the receiving environmental compartment, resulting in an effective input of 0.96 ± 0.35 kg/capita of rubber into the natural environment. Most of this mass (74%) was deposited on roadside soils (up to 5 m distance from road), 22% flowed into surface waters and the remaining part (4%) was emitted to soils. The amount of tyre wear particles emitted to the aquatic environment was stated to depend on the infrastructure for collection and treatment of road runoff.

The concentrations and removal efficiencies of DPG was measured in three municipal STPs in China (Zhang, 2023). DPG (maximum concentration of 3570 ng/L) was the compound with the highest concentration among the 23 tyres additives analysed and showed a detection frequency of 100%. Two out of three STP analysed showed a removal of the substance between 88.5-96.8%. In one of the three STP the removal rates of DPG were negative, indicating that the substance was not efficiently removed.

Mobile substances such as DPG might not be effectively removed in wastewater. A mobile substance as the intrinsic property to spread quickly in the aquatic environment to the source of our drinking water. Sewer residence time (the amount of time a given volume of wastewater resides in a sewer system prior to treatment) can have a significant influence on predictions of environmental fate and transport of wastewater constituents and corresponding risk assessment. The mobility assessment is based on experimentally determined log organic carbon - water partition coefficients (log Koc). The CLP amendment including new hazard classes stipulates that a substance shall be considered to fulfil the mobility criterion (M) when the log Koc is less than 3[[22]](#footnote-23). According to the OECD 106 study (Adsorption-Desorption using a batch equilibrium method, unpublished study report 2015) the experimental adsorption coefficient log Koc values measured on five soil ranged from 2.5 to 3.13 for DPG with four soils displaying log Koc < 3. The QSAR model KOCWIN adsorption coefficient is estimated to 2.4 and 3.2 depending of the model. For mobile or very mobile substances, if the residence time in WWTP is too short these substance will not be removed efficiently before being release to the environment.

Altogether, this literature review confirms the occurrence and widespread distribution of DPG in the aquatic compartment. The monitoring values are under the hazard threshold values (PNEC values) for the aquatic environment, at the exception of intermittent rainfall event. There is however an uncertainty whether the available surface water monitoring data represent local assessment (as closely as possible to the emission source). Also, the mobility property of DPG needs to be considered as it might not be efficiently removed from the WWTP (including domestic or municipal sewage treatment plants-STP or industrial wastewater treatment plants). Monitoring the influent and effluent concentration of DPG at the WWTP could help understand the fate and behaviour of the substance. The higher concentration of DPG found in monitoring data from WWTP compared to the other aquatic environment raised the question if the exposure scenarios proposed by the Registrants cover all the uses of DPG and exposure route of DPG from rubber articles. In particular, the release of DPG from high density polyethylene (HDPE) pipe material is of concern.

# Risk characterisation

## Human health

Risk characterisation was performed based on exposure assessed in the exposure scenarios of the registration dossiers and on the DNEL recommended by the aMSCA considering the recent EOGRTS study as discussed in section 1.4.2.

Table 26: Human health risk characterisation

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | Exposure scenario name | | Contributing scenario | PROC | RCR | RMM | Exposure model |
| Manufacture of DPG | | | | | | | |
| 1a | Manufacture of substances - Registrant 1 | | CS 6 | 8a | RCR Dermal =0.949  RCR Combined route =0.954 | Basic room ventilation (up to 3 ACH)  Advanced Occupational Health and Safety Management System  95% Dermal protection effectiveness  Eye protection  Respiratory protection (APF = 20) | Riskofderm 2.0, TRA Workers 3.0, ART 1.5 |
| CS 7 | 8a | RCR Dermal = 0.963  RCR Combined route =0.965 | Basic room ventilation (up to 3 ACH)  Advanced Occupational Health and Safety Management System  95% Dermal protection effectiveness  Eye protection  Respiratory protection (APF = 20) | TRA Workers 3.0, ART 1.5 |
| CS 13 | 9 | RCR Dermal = 1.219  RCR Combined route =1.254 | Basic room ventilation (up to 3 ACH)  Local exhaust ventilation: specifically designed fixed capturing hood, on tool extraction or enclosing hoods (assumed effectiveness = 90-95%)  Advanced Occupational Health and Safety Management System  95% Dermal protection effectiveness  Eye protection  Respiratory protection (APF = 20) | TRA Workers 3.0, ART 1.5 |
| CS 14 | 9 | RCR Dermal = 1.219  RCR Combined route =1.227 | Basic room ventilation (up to 3 ACH)  Local exhaust ventilation: specifically designed fixed capturing hood, on tool extraction or enclosing hoods (assumed effectiveness = 90-95%)  Advanced Occupational Health and Safety Management System  95% Dermal protection effectiveness  Eye protection  Respiratory protection (APF = 20) | TRA Workers 3.0, ART 1.5 |
| CS 22 | 22 | RCR Combined route =1.01 | Basic room ventilation (up to 3 ACH)  Advanced Occupational Health and Safety Management System  95% Dermal protection effectiveness  Eye protection  Respiratory protection (APF = 40) Air-purifying Full-Face (with gas/cartridge-cartridge, that can be combined with a  particulate filter) (APF 40) | TRA Workers 3.0 |
| 1b | Manufacture of substances - Registrant 2 | | CS 6 | 14 | RCR Combined route =1.116 | Basic room ventilation (up to 3 ACH)  Advanced Occupational Health and Safety Management System  95% Dermal protection effectiveness | TRA Workers 3.0 |
| CS 7 | 3 | RCR Dermal =1.471  RCR combined routes = 1.484 | Basic room ventilation (up to 3 ACH)  Local exhaust ventilation: specifically designed fixed capturing hood, on tool extraction or enclosing hoods (assumed effectiveness >= 90-95%)  Advanced Occupational Health and Safety Management System  Closed batch process with occasional controlled exposure | TRA Workers 3.0 |
| CS 8 | 8a | RCR dermal = 0.949  RCR combined routes = 0.954 | Basic room ventilation (up to 3 ACH)  Advanced Occupational Health and Safety Management System  Respiratory protection: Yes (APF >= 20)  95% dermal protection effectiveness | TRA Workers 3.0  Riskofderm 2.0; ART 1.5 |
| CS 9 | 8a | RCR dermal = 0.964  RCR combined routes = 0.965 | Basic room ventilation (up to 3 ACH)  Advanced Occupational Health and Safety Management System  Respiratory protection: Yes (APF >= 20)  95% dermal protection effectiveness | TRA Workers 3.0  Riskofderm 2.0; ART 1.5 |
| CS 13 | 8b | RCR dermal = 1.461  RCR combined routes = 1.476 | Basic room ventilation (up to 3 ACH)  Local exhaust ventilation: enclosing hood with very high effectiveness such as fume cupboard (assumed effectiveness >= 95%)  Advanced Occupational Health and Safety Management System  95% dermal protection effectiveness  Eye protection  No respiratory protection, however, a dry substance silo (reservoir) is connected to a filling device with extraction (fabric filter sleeves), so under standard operating conditions the respiratory protection is not necessary. | TRA Workers 3.0 |
| CS 17 | 21 | RCR dermal = 1.012  RCR combined routes = 1.515 | Basic room ventilation (up to 3 ACH)  Advanced Occupational Health and Safety Management System  95% dermal protection effectiveness  Eye protection  Respiratory protection: APF >= 10 | TRA Workers 3.0 |
| CS 18 | 21 | RCR inhalation = 0.91  RCR combined routes = 1.414 | Basic room ventilation (up to 3 ACH)  Advanced Occupational Health and Safety Management System  95% dermal protection effectiveness  Eye protection  Respiratory protection: APF >= 10 | TRA Workers 3.0 |
|  | | Formulation and re- packaging | | | | | |
| 2 | Formulation or re-packing - Manufacture of Masterbatches - continuous process | | CS 3 | 3 | RCR Dermal = 1.219  RCR Combined route =1.236 | Good room ventilation (3 to 5 ACH)  Local exhaust ventilation: specifically designed fixed capturing hood, on tool extraction or enclosing hoods (assumed effectiveness = 90-95%)  Advanced Occupational Health and Safety Management System  95% Dermal protection effectiveness  Eye protection  Respiratory protection (APF = 20) | TRA Workers 3.0 |
| CS 15 | 15 | RCR Dermal = 1.461  RCR Combined route =1.471 | Good room ventilation (3 to 5 ACH)  Advanced Occupational Health and Safety Management System  95% Dermal protection effectiveness  Eye protection  Respiratory protection (APF = 20) | TRA Workers 3.0 |
| 3 | Formulation or re-packing - Masterbatch production - internal mixer | | CS 4 | 5 | RCR Dermal = 0.974  RCR Combined route =1.223 | Basic room ventilation (up to 3 ACH)  Local exhaust ventilation: specifically designed fixed capturing hood, on tool extraction or enclosing hoods (assumed effectiveness = 90-95%)  Advanced Occupational Health and Safety Management System  80% Dermal protection effectiveness  Eye protection | TRA Workers 3.0 |
| CS 5 | 14 | RCR Dermal = 1.219  RCR Combined route =1.221 | Basic room ventilation (up to 3 ACH)  Local exhaust ventilation: specifically designed fixed capturing hood, on tool extraction or enclosing hoods (assumed effectiveness = 90-95%)  Advanced Occupational Health and Safety Management System  Eye protection | TRA Workers 3.0 |
| 4 | Formulation and re-packaging. | | CS 2 | 8a | RCR Combined route =1.373 | Good room ventilation (3 to 5 ACH)  Local exhaust ventilation: specifically designed fixed capturing hood, on tool extraction or enclosing hoods (assumed effectiveness = 90-95%)  Advanced Occupational Health and Safety Management System  90% Dermal protection effectiveness  Eye protection  Respiratory protection (APF = 20) | TRA Workers 3.0 |
| CS 7 | 8a | RCR Combined route =1.373 | Basic room ventilation (up to 3 ACH)  Local exhaust ventilation: specifically designed fixed capturing hood, on tool extraction or enclosing hoods (assumed effectiveness = 90-95%)  Advanced Occupational Health and Safety Management System  90% Dermal protection effectiveness  Eye protection  Respiratory protection (APF = 10) | TRA Workers 3.0 |
| CS 11 | 9 | RCR Dermal = 0.975  RCR Combined route =0.98 | Basic room ventilation (up to 3 ACH)  Local exhaust ventilation: specifically designed LEV such as receiving hoods (assumed effectiveness = 80-90%)  Basic Occupational Health and Safety Management System  80% Dermal protection effectiveness  Eye protection | TRA Workers 3.0 |
| CS 12 | 9 | RCR Dermal = 0.975  RCR Combined route =0.98 | Basic room ventilation (up to 3 ACH)  Local exhaust ventilation: specifically designed LEV such as receiving hoods (assumed effectiveness = 80-90%)  Basic Occupational Health and Safety Management System  80% Dermal protection effectiveness  Eye protection  Respiratory protection (APF = 10) | TRA Workers 3.0 |
| 13 | Formulation or re-packing - End of Life Tyre: Coarse shredding | | CS 2 | 8a | RCR Dermal = 0.974  RCR Combined route =1.227 | Basic room ventilation (up to 3 ACH)  Advanced Occupational Health and Safety Management System  80% Dermal protection effectiveness | TRA Workers 3.0 |
| CS 3 | 8b | RCR Dermal = 0.974  RCR Combined route =1.2025 | Basic room ventilation (up to 3 ACH)  Advanced Occupational Health and Safety Management System  80% Dermal protection effectiveness | TRA Workers 3.0 |
| CS 4 | 8b | RCR Dermal = 1, 005  RCR Combined route =1.51 | Basic room ventilation (up to 3 ACH)  Advanced Occupational Health and Safety Management System | TRA Workers 3.0 |
| 14 | Formulation or re-packing - End of life Tyre: Grinding (ambient) | | / |  | / |  |  |
| 15 | Formulation or re-packing - End of Life Tyre: Grinding cryogenic | | CS 2 | 8a | RCR Dermal = 0.974  RCR Combined route =1.227 | Basic room ventilation (up to 3 ACH)  Advanced Occupational Health and Safety Management System  80% Dermal protection effectiveness | TRA Workers 3.0 |
| CS 3 | 8b | RCR Dermal = 0.974  RCR Combined route =0.975 | Basic room ventilation (up to 3 ACH)  Advanced Occupational Health and Safety Management System  80% Dermal protection effectiveness  Respiratory protection (AFP 10) | TRA Workers 3.0 |
| 16 | Formulation or re-packing - End of Life Tyre: Pyrolysis | | CS 2 | 8b | RCR Dermal = 0.974  RCR Combined route =1.025 | Basic room ventilation (up to 3 ACH)  Advanced Occupational Health and Safety Management System  80% Dermal protection effectiveness | TRA Workers 3.0 |
| 17 | Formulation or re-packing - End of Life Tyre: Energy recovery: cement kiln | | CS 2 | 8b | RCR Dermal = 0.974  RCR Combined route =1.025 | Basic room ventilation (up to 3 ACH)  Advanced Occupational Health and Safety Management System  80% Dermal protection effectiveness | TRA Workers 3.0 |
| CS 3 | 21 | RCR Dermal = 1.005  RCR Combined route =1.511 | Basic room ventilation (up to 3 ACH)  Advanced Occupational Health and Safety Management System | TRA Workers 3.0 |
| 18 | Formulation or re-packing - End of Life Tyre: Energy recovery: other | | CS 2 | 8b | RCR Dermal = 0.974  RCR Combined route =1.025 | Basic room ventilation (up to 3 ACH)  Advanced Occupational Health and Safety Management System  80% Dermal protection effectiveness | TRA Workers 3.0 |
| 19 | Formulation or re-packing - End of Life Tyre: Electric arc furnace | | CS 2 | 8b | RCR Dermal = 0.974  RCR Combined route =1.025 | Basic room ventilation (up to 3 ACH)  Advanced Occupational Health and Safety Management System  80% Dermal protection effectiveness | TRA Workers 3.0 |
| 20 | Formulation or re-packing - End of Life Tyre: Devulcanization/reclaim | | CS 2 | 8b | RCR Dermal = 0.974  RCR Combined route =1.025 | Basic room ventilation (up to 3 ACH)  Advanced Occupational Health and Safety Management System  80% Dermal protection effectiveness | TRA Workers 3.0 |
|  | | Use at industrial sites | | | |  |  |
| 5 | Use at industrial sites - Manufacture of General Rubber Goods (Grad PD, C, GC & Mixland) - According to ETRMA. | | CS 4 | 9 | RCR dermal = 1.46  RCR Combined route = 1.49 | Basic room ventilation (up to 3 ACH)  Local exhaust ventilation: specifically designed fixed capturing hood, on tool extraction or enclosing hoods (assumed effectiveness = 90-95%)  Advanced occupational Health and Safety Management System  Eye protection | TRA Workers 3.0 |
| CS 5 | 9 | Combined route RCR = 1.04 | Basic room ventilation (up to 3 ACH)  Advanced occupational Health and Safety Management System  95% dermal protection effectiveness  Eye protection | TRA Workers 3.0 |
| CS 6 | 9 | RCR Inhalation = 1.01  RCR Combined route = 1.50 | Basic room ventilation (up to 3 ACH)  Local exhaust ventilation: specifically designed fixed capturing hood, on tool extraction or enclosing hoods (assumed effectiveness = 90-95%)  Advanced occupational Health and Safety Management System  90% dermal protection effectiveness  Eye protection  Respiratory protection (APF = 10) | TRA Workers 3.0 |
| CS 9 | 5 | RCR Dermal = 0.973  RCR Combined route = 1.61 | Basic room ventilation (up to 3 ACH)  Local exhaust ventilation: specifically designed fixed capturing hood, on tool extraction or enclosing hoods (assumed effectiveness = 90-95%)  Advanced occupational Health and Safety Management System  80% dermal protection effectiveness  Eye protection  Respiratory protection (APF = 20) | TRA Workers 3.0 |
| CS 10 | 5 | RCR Dermal = 0.974  RCR Combined route = 1.61 | Basic room ventilation (up to 3 ACH)  Local exhaust ventilation: specifically designed fixed capturing hood, on tool extraction or enclosing hoods (assumed effectiveness = 90-95%)  Advanced occupational Health and Safety Management System  90% dermal protection effectiveness  Eye protection  Respiratory protection (APF = 10) | TRA Workers 3.0 |
| CS 12 | 9 | RCR Inhalation = 1.01  RCR Combined routes = 1.50 | Basic room ventilation (up to 3 ACH)  Local exhaust ventilation: specifically designed fixed capturing hood, on tool extraction or enclosing hoods (assumed effectiveness = 90-95%)  Advanced occupational Health and Safety Management System  90% dermal protection effectiveness  Eye protection  Respiratory protection (APF = 10) | TRA Workers 3.0 |
| CS 17 | 8b | RCR Dermal =1.461  RCR Combined routes =1.476 | Basic room ventilation (up to 3 ACH)  Local exhaust ventilation: enclosing hood with very high effectiveness such as fume cupboard (assumed effectiveness = 95%)  Advanced occupational Health and Safety Management System  Eye protection | TRA Workers 3.0 |
| CS 18 | 5 | RCR Dermal = 0.974  RCR Combined route = 1.42 | Basic room ventilation (up to 3 ACH)  Local exhaust ventilation: Yes, specifically designed fixed capturing hood, on tool extraction or enclosing hoods (assumed effectiveness = 90-95%)  Advanced occupational Health and Safety Management System  Eye protection  Respiratory protection (APF = 10) | TRA Workers 3.0 |
| CS 19 | 9 | RCR Dermal = 0.974  RCR Combined routes = 1.42 | Basic room ventilation (up to 3 ACH)  Local exhaust ventilation: Yes, specifically designed fixed capturing hood, on tool extraction or enclosing hoods (assumed effectiveness = 90-95%)  Advanced occupational Health and Safety Management System  Eye protection  Respiratory protection (APF = 10) | TRA Workers 3.0 |
| CS 20 | 9 | RCR Combined routes =0.932 | Basic room ventilation (up to 3 ACH)  Local exhaust ventilation: Yes, specifically designed fixed capturing hood, on tool extraction or enclosing hoods (assumed effectiveness = 90-95%)  Advanced occupational Health and Safety Management System  Eye protection  Respiratory protection (APF = 10) | TRA Workers 3.0 |
| CS 21 | 9 | RCR dermal = 0.98  RCR Combined routes= 1.08 | Basic room ventilation (up to 3 ACH)  Advanced occupational Health and Safety Management System  Eye protection | TRA Workers 3.0 |
| CS 22 | 9 | RCR Dermal = 1.22  RCR Combined routes = 1.27 | Basic room ventilation (up to 3 ACH)  Advanced occupational Health and Safety Management System  95% dermal protection effectiveness  Eye protection  Respiratory protection (APF = 10) | TRA Workers 3.0 |
| CS 23 | 9 | RCR Dermal = 0.975  RCR Combined routes= 1.08 | Basic room ventilation (up to 3 ACH)  Advanced occupational Health and Safety Management System  95% dermal protection effectiveness  Eye protection | TRA Workers 3.0 |
| CS 24 | 10 | RCR dermal = 0.975  RCR combined routes = 1.03 | Basic room ventilation (up to 3 ACH)  Local exhaust ventilation: specifically designed fixed capturing hood, on tool extraction or enclosing hoods (assumed effectiveness = 90-95%)  Advanced occupational Health and Safety Management System  95% dermal protection effectiveness  Eye protection | TRA Workers 3.0 |
| CS 25 | 13 | RCR dermal = 0.97  RCR combined route = 1.08 | Basic room ventilation (up to 3 ACH)  Advanced occupational Health and Safety Management System  90% dermal protection effectiveness  Eye protection | TRA Workers 3.0 |
| CS 26 | 10 | RCR dermal = 0.975  RCR combined route = 1.03 | Basic room ventilation (up to 3 ACH)  Local exhaust ventilation: specifically designed fixed capturing hood, on tool extraction or enclosing hoods (assumed effectiveness = 90-95%)  Advanced occupational Health and Safety Management System  95% dermal protection effectiveness  Eye protection | TRA Workers 3.0 |
| CS 31 | 10 | RCR dermal = 0.975  RCR combined routes= 1.075 | Basic room ventilation (up to 3 ACH)  Local exhaust ventilation: specifically designed fixed capturing hood, on tool extraction or enclosing hoods (assumed effectiveness = 90-95%)  Advanced occupational Health and Safety Management System  95% dermal protection effectiveness  Eye protection  Respiratory protection (APF = 10) | TRA Workers 3.0 |
| CS 35 | 10 | RCR dermal = 0.975  RCR combined routes = 1.48 | Basic room ventilation (up to 3 ACH)  Advanced occupational Health and Safety Management System  95% dermal protection effectiveness  Eye protection | TRA Workers 3.0 |
| 8 | Use at industrial sites - pre-step tyre -- manufacturing and handling of DPG grad C // masterbatch | | CS 2 | 5 | RCR inhalation = 1.112  RCR combined routes = 1.6 | Basic Room ventilation (up to 3 ACH)  Local exhaust ventilation: specifically designed fixed capturing hood, on tool extraction or enclosing hoods (assumed effectiveness = 90-95%)  Advanced occupational Health and Safety Management System  90% dermal protection effectiveness  Eye protection  Respiratory protection (APF = 20) | TRA Workers 3.0 |
| CS 3 | 14 | RCR dermal = 1,219  RCR combined routes =1,224 | Basic Room ventilation (up to 3 ACH)  Local exhaust ventilation: specifically designed fixed capturing hood, on tool extraction or enclosing hoods (assumed effectiveness = 90-95%)  Advanced occupational Health and Safety Management System  Eye protection  Respiratory protection (APF = 10) | TRA Workers 3.0 |
| 9 | Use at industrial sites - Manufacture of Tyres (Grad PD, C, GC & Mixland) | | CS 2 | 9 | RCR combined routes = 0,912 | Good Room ventilation (3 to 5 ACH)  Local exhaust ventilation: specifically designed fixed capturing hood, on tool extraction or enclosing hoods (assumed effectiveness = 90-95%) Dilution ventilation  Advanced occupational Health and Safety Management System  80% dermal protection effectiveness  Eye protection  Respiratory protection (APF = 10) | TRA Workers 3.0 |
| CS 4 | 9 | RCR dermal = 1.46  RCR combined routes = 1.492 | Basic room ventilation (up to 3 ACH)  Local exhaust ventilation: specifically designed fixed capturing hood, on tool extraction or enclosing hoods (assumed effectiveness = 90-95%) Dilution ventilation  Advanced occupational Health and Safety Management System  Eye protection | TRA Workers 3.0 |
| CS 5 | 9 | RCR combined routes = 1.035 | Basic Room ventilation (up to 3 ACH)  Advanced occupational Health and Safety Management System  95% dermal protection effectiveness  Eye protection | TRA Workers 3.0 |
| CS 6 | 9 | RCR inhalation= 1.012  RCR combined routes = 1.50 | Basic Room ventilation (up to 3 ACH)  Local exhaust ventilation: specifically designed fixed capturing hood, on tool extraction or enclosing hoods (assumed effectiveness = 90-95%)  Advanced occupational Health and Safety Management System  80% dermal protection effectiveness  Eye protection  Respiratory protection (APF = 10) | TRA Workers 3.0 |
| CS 9 | 9 | RCR dermal = 1.219  RCR combined routes = 1.269 | Basic Room ventilation (up to 3 ACH)  Advanced occupational Health and Safety Management System  95% dermal protection effectiveness  Eye protection  Respiratory protection (APF = 10) | TRA Workers 3.0 |
| CS 10 | 9 | RCR inhalation = 1.012  RCR combined routes = 1.5 | Basic Room ventilation (up to 3 ACH)  Local exhaust ventilation: specifically designed fixed capturing hood, on tool extraction or enclosing hoods (assumed effectiveness = 90-95%)    Advanced occupational Health and Safety Management System  80% dermal protection effectiveness  Eye protection  Respiratory protection (APF = 10) | TRA Workers 3.0 |
| CS 13 | 9 | RCR inhalation = 1.219  RCR combined routes= 1.269 | Basic Room ventilation (up to 3 ACH)  Advanced occupational Health and Safety Management System  95% dermal protection effectiveness  Eye protection  Respiratory protection (APF = 10) | TRA Workers 3.0 |
| CS 14 | 8b | RCR combined routes= 1.373 | Good Room ventilation (3 to 5 ACH)  Local exhaust ventilation: enclosing hood with very high effectiveness such as fume cupboard (assumed effectiveness = 95%)  Advanced occupational Health and Safety Management System  80% dermal protection effectiveness  Eye protection | TRA Workers 3.0 |
| CS 17 | 8b | RCR dermal = 0.974  RCR combined routes =1.075 | Basic Room ventilation (up to 3 ACH)  Advanced occupational Health and Safety Management System  90% dermal protection effectiveness  Eye protection | TRA Workers 3.0 |
| CS 18 | 5 | RCR dermal = 0.974  RCR combined routes = 1.42 | Basic Room ventilation (up to 3 ACH)  Local exhaust ventilation: specifically designed fixed capturing hood, on tool extraction or enclosing hoods (assumed effectiveness = 90-95%)  Advanced occupational Health and Safety Management System  Eye protection  Respiratory protection (APF = 10) | TRA Workers 3.0 |
| CS 19 | 5 | RCR dermal = 0.974  RCR combined routes = 1.42 | Basic Room ventilation (up to 3 ACH)  Local exhaust ventilation: specifically designed fixed capturing hood, on tool extraction or enclosing hoods (assumed effectiveness = 90-95%)  Advanced occupational Health and Safety Management System  Eye protection  Respiratory protection (APF = 10) | TRA Workers 3.0 |
| CS 20 | 9 | RCR combined routes =0.932 | Basic Room ventilation (up to 3 ACH)  Local exhaust ventilation: specifically designed fixed capturing hood, on tool extraction or enclosing hoods (assumed effectiveness = 90-95%)  Advanced occupational Health and Safety Management System  Eye protection  Respiratory protection (APF = 10) | TRA Workers 3.0 |
| CS 21 | 9 | RCR dermal = 0.975  RCR combined routes =1.075 | Basic Room ventilation (up to 3 ACH)  Advanced occupational Health and Safety Management System  80% dermal protection effectiveness  Eye protection | TRA Workers 3.0 |
| CS 22 | 9 | RCR dermal = 0.975  RCR combined routes =1.075 | Basic Room ventilation (up to 3 ACH)  Advanced occupational Health and Safety Management System  80% dermal protection effectiveness  Eye protection | TRA Workers 3.0 |
| CS 24 | 10 | RCR dermal = 0.975  RCR combined routes = 1 | Basic Room ventilation (up to 3 ACH)  Local exhaust ventilation: specifically designed fixed capturing hood, on tool extraction or enclosing hoods (assumed effectiveness = 90-95%)  Advanced occupational Health and Safety Management System  Eye protection  90 % dermal protection effectiveness | TRA Workers 3.0 |
| CS 25 | 10 | RCR dermal = 0.975  RCR combined routes = 1.227 | Basic Room ventilation (up to 3 ACH)  Advanced occupational Health and Safety Management System  Eye protection  90 % dermal protection effectiveness | TRA Workers 3.0 |
| CS 29 | 10 | RCR dermal = 0.975  RCR combined routes =1.227 | Basic Room ventilation (up to 3 ACH)  Advanced occupational Health and Safety Management System  Eye protection  90 % dermal protection effectiveness | TRA Workers 3.0 |
| CS 30 | 21 | RCR inhalation = 1.01  RCR combined routes =1.414 | Basic Room ventilation (up to 3 ACH)  Advanced occupational Health and Safety Management System  Eye protection  80 % dermal protection effectiveness | TRA Workers 3.0 |
| CS 33 | 10 | RCR dermal = 0.975  RCR combined routes =1.227 | Basic Room ventilation (up to 3 ACH)  Local exhaust ventilation: specifically designed fixed capturing hood, on tool extraction or enclosing hoods (assumed effectiveness = 90-95%)  Advanced occupational Health and Safety Management System  Eye protection  90 % dermal protection effectiveness | TRA Workers 3.0 |
| CS 37 | 10 | RCR dermal = 0.975  RCR combined routes = 1 | Basic Room ventilation (up to 3 ACH)  Local exhaust ventilation: specifically designed fixed capturing hood, on tool extraction or enclosing hoods (assumed effectiveness = 90-95%)  Advanced occupational Health and Safety Management System  Eye protection  90 % dermal protection effectiveness | TRA Workers 3.0 |
|  | | Article service life – professional workers | | | | | |
| 6 | Service life (professional worker) - GRG articles - conveyor belt | | CS 2 | 21 | RCR dermal = 1.01  RCR combined routes = 1.01 | Basic room ventilation (up to 3 ACH)  Basic occupational Health and Safety Management System  Eye protection | TRA Workers 3.0 |
| 10 | Service life (professional worker) - Garage owner - tyres change. | | CS 2 | 21 | / | / | / |
| 12 | Service life (professional worker) - End of Life Tyre: ELT pre-processing  storage. | | CS2 | 21 | RCR dermal = 1.001  RCR combined routes = 1.156 | Basic room ventilation (up to 3 ACH)  Basic occupational Health and Safety Management System  Respiratory protection (APF = 10) | TRA Workers 3.0 |
| CS 3 | 21 | RCR dermal = 1.005  RCR combined routes = 1.31 | Basic room ventilation (up to 3 ACH)  Local exhaust ventilation: specifically designed LEV such as receiving hoods (assumed effectiveness  = 80-90%)  Basic occupational Health and Safety Management System | TRA Workers 3.0 |
| 21 | Service life (professional worker) - ELT articles – installation of shock  absorbing tiles | | CS 2 | 21 | RCR inhalation = 1.062  RCR combined routes = 1.264 | Basic room ventilation (up to 3 ACH)  Basic occupational Health and Safety Management System  80% Dermal protection effectiveness | TRA Workers 3.0 |
| 23 | Service life (professional worker) – re-use of ELT articles – installation of synthetic turf  fields | | CS 2 | 21 | RCR inhalation = 1.062  RCR combined routes = 1.264 | Basic room ventilation (up to 3 ACH)  Basic occupational Health and Safety Management System  80% Dermal protection effectiveness | TRA Workers 3.0 |
| CS 3 | 21 | RCR dermal = 1.01  RCR combined routes = 1.112 | Basic room ventilation (up to 3 ACH)  Basic occupational Health and Safety Management  Respiratory protection (APF = 10) | TRA Workers 3.0 |
|  | | Article service life – consumers | | | | | |
| 7 | **Service life (consumers) - GRG articles (balloons) – consumer**  **(children’s 6 to 11 years)** | |  | / | | | |
| 11 | **Service life (consumers) - Consumer use of tyres (vehicles).** | | CS 2 | / | RCR dermal = 1.124  RCR combined routes = 1.132 | / | TRA Consumers 3.1  (R15)  Exposure time per event: = 1 h/event  Frequency of use over a year: Infrequent |
| 22 | **Service life (consumers) - ELT articles - shock absorbing tiles** **(children’s < 3 years)** | | CS 2 |  | / | | |
| 24 | **Service life (consumers) - ELT articles - synthetic turf fields**  (**children’s 6 to 11 years)** | | CS 2 |  | / | | |

The exposure scenarios, the associated PROCs and the calculated risks are detailed in tables 21 and 26 in annex I. Only the scenarios with RCRs > 1 (highlighted in red) and the scenarios with RCRs close to 1 (0.95≤RCR<1) (highlighted in orange) are reported in the table. The associated risk management measures (RMM) and the exposure models used to determine the risks are reported.

Overall, RCR > 1 are observed in contributing scenario of most exposure scenario for industrial and professional workers and in one scenario for consumers.

For industrial workers, contributing scenario leading to RCR > 1 were identified for PROC 3, 5, 8a, 8b, 9, 10, 13, 14, 15, 21 and 22 in several exposure scenarios. The RCRs calculated were between >1 and 1.61.

Considering professional workers, contributing scenario with RCR > 1 were identified for PROC 21 for:

* exposure scenario 6 (Service life (professional worker) - GRG articles - conveyor belt),
* exposure scenario 12 (Service life (professional worker) - End of Life Tyre: ELT pre-processing storage.),
* exposure scenario 21 (Service life (professional worker) - ELT articles – installation of shock absorbing tiles)
* exposure scenario 23 (Service life (professional worker) – re-use of ELT articles – installation of synthetic turf fields).

The RCRs calculated were between >1 and 1.31.

For consumers, the contributing scenario 2 of the exposure scenario 11 (Service life (consumers) - Consumer use of tyres (vehicles)) present a RCR for dermal route equal to 1.12 and a RCR for combined routes equal to 1.13. The situation considered for RCR calculation was a worst case situation of new tyre change (higher % of DPG compare to used tyre) with a % of DPG value of 0.08 (% of DPG in full new tyre). DPG in used tyres is considered to be 0.04%. In this scenario, only the Tier I tool ECETOC TRA has been used. On the other hand, no data have been located by the aMSCA to confirm the concentration of DPG present in tyres, whether manufactured in Europe or imported from outside Europe.

**Risk characterization based on literature data:**

It is highlighted that data are scarce and have limitations. These calculations are therefore performed to obtain an estimates whether risks may occur through the different reported sources of exposures.

**Drinking water:**

Risk calculation was performed based on publications where a specific concentration of DPG was clearly indicated.

In Gollong *et al*. (2022), the concentration indicated is probably a median of DPG concentrations in all the types of water tested in the study and therefore not specific to drinking water samples.

In Neuwald *et al*. (2022), the concentration of DPG was calculated in sources of drinking water and not in the treated water.

In Tang *et al*. (2015), the maximum DPG concentration in the residential district has been selected (0.47 mg/L) for risk estimation.

The exposure assessment is based on the following calculation method (Anses, 2018):

Exposure = Cwater x consumption/ bw

Where:

**Exposure:** µg/kg bw/d

**Cwater:** concentration of DPG in water in µg/L

**Consumption:** 2L/d for adults, 1L/d for children, 0.75 L/d for infants (WHO, 2022)

**bw:** 60 kg for adults, 10 kg for children, 5 kg for infants (WHO, 2022)

**Table 27: Exposure and risk characterisation in drinking water**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Publications | Concentrations of DPG (µg/L) | Concentration type | Exposure (µg/kg bw/d) | | DNELoral (µg/kg bw/d) | Risk characterization | |
| Gollong et al. 2022 | 4.10-3 | Median concentration | Adults | 1.33.10-4 | 10 | Adults | 1.33.10-5 |
| Children | 4.10-4 | Children | 4.10-5 |
| Infants | 6.10-4 | Infants | 6.10-5 |
| Tang et al. 2015 | 470 | Maximal concentration | Adults | 15.67 | Adults | 1.567 |
| Children | 47 | Children | 4.7 |
| Infants | 70.5 | Infants | 7.05 |
| Neuwald et al. 2022 | 1.7.10-4 | Median concentration | Adults | 5.67.10-6 | Adults | 5.67.10-7 |
| Children | 1.7.10-5 | Children | 1.7.10-6 |
| Infants | 2.55.10-5 | Infants | 2.55.10-6 |

Overall, risks were highlighted when the maximal DPG concentration from the Tang *et al*. (2015) study was considered. In this study, DPG is found to be migrating from high density polyethylene (HDPE) pipe material used for water distribution. It is important to note that there are significant disparities in DPG concentrations between the different publications.

**Dust ingestion:**

Risk estimation was performed for the publication below in where an exposure assessment to DPG was conducted.

Li & Kannan (2023) assessed human exposure to DPG through dust ingestion and the following ranges were 0.07−4.40, 0.09−5.20, 0.03−1.70, 0.02−1.04, and 0.01−0.87 ng/kg body weight (BW)/day for infants, toddlers, children, teenagers, and adults, respectively. These exposure are all below the DNEL recommended by aMSCA. Concentrations reported in other studies (Tan *et al*., 2021 and Shin *et al*., 2020) were in the same range of concentrations.

## Environmental risk assessment based on exposure scenarios of the registration dossier

LOCAL assessment

The local Predicted Exposure Concentrations (PECs) reported for each contributing scenario correspond to the sum of the local concentrations (Clocal) and the regional concentrations (PEC regional). The table below presents the aMSCA’s conclusion of the environmental risk assessment for each exposure scenario.

**Table 28: Environmental risk assessment and conclusion**

|  |  |  |  |
| --- | --- | --- | --- |
| **ENV compartment** | **Local Predicted Exposure concentration (PEC)** | **RCR value** | **Conclusion** |
| **ES 1a** | M - Manufacture of the substance – Registrant 1 | | |
| Sewage Treatment Plant | NR | NR | NR |
| Fresh water | 1.15E-01mg.l-1 | **RCR = 3.83** | **Unacceptable** |
| Sediment (fresh water) | 2.11 mg.kg-1 | **RCR = 3.86** | **Unacceptable** |
| Agricultural soil | NR | NR | NR |
| Groundwater | NR |  | |
| **ES 1b** | M - Manufacture of the substance – Registrant 2 | | |
| Sewage Treatment Plant | 7.07E-01 mg.l-1 | RCR = 4.81E-01 | Acceptable |
| Fresh water | 7.17E-04 mg.l-1 | RCR = 2.39E-02 | Acceptable |
| Sediment (fresh water) | 1.74E-02 mg.kg-1 | RCR = 3.19E-02 | Acceptable |
| Agricultural soil | 2.47 mg.kg-1 | **RCR =6.91** | **The registrant mentioned that no application of the STP sludge is made on agricultural soil** |
| Groundwater | **56.3 µg/l** | **NR if no application of the STP sludge is made on agricultural soil.** | |
| **ES 2** | F - Formulation or re-packing – Masterbatches manufacturel- Mixland | | |
| Sewage Treatment Plant | NR | NR | NR |
| Fresh water | 1.28 mg.l-1 | **RCR =42.6** | **Unacceptable** |
| Sediment (fresh water) | 23.4 mg.kg-1 | **RCR= 42.9** | **Unacceptable** |
| Agricultural soil | NR | NR | NR |
| Groundwater | NR |  | |
| **ES 3** | F - Formulation or re-packing - Masterbatch production - internal mixture from grad C | | |
| Sewage Treatment Plant | NR | NR | NR |
| Fresh water | 1.79 mg.l-1 | **RCR =59.7** | **Unacceptable** |
| Sediment (fresh water) | 32.8 mg.kg-1 | **RCR = 60.1** | **Unacceptable** |
| Agricultural soil | NR | NR | NR |
| Groundwater | NR |  | |
| **ES 4** | F - Formulation or re-packing - Formulation and repackaging (grad PD or C) | | |
| Sewage Treatment Plant | NR | NR | NR |
| Fresh water | 15.3 mg.l-1 | **RCR =511.4** | **Unacceptable** |
| Sediment (fresh water) | 2.81E+02 mg.kg-1 | **RCR = 515.2** | **Unacceptable** |
| Agricultural soil | NR | NR | NR |
| Groundwater | NR |  | |
| **ES 5** | M - Manufacture of General Rubber Goods (Grad PD, C, GC & Mixland) | | |
| Sewage Treatment Plant | 7.54E-04 mg.l-1 | RCR = 5.13E-04 | Acceptable |
| Fresh water | 1.41E-04 mg.l-1 | RCR = 4.69E-03 | Acceptable |
| Sediment (fresh water) | 6.84E-03 mg.kg-1 | RCR = 1.25E-02 | Acceptable |
| Agricultural soil | 1.96E-03 mg.kg-1 | RCR = 5.48E-03 | Acceptable |
| Groundwater | 4.17E-02 µg/l |  | |
| **ES 6** | SL (professional worker) - GRG articles - conveyor belt | | |
| Sewage Treatment Plant | 5.24E-06 mg.l-1 | RCR = 3.57E-06 | Acceptable |
| Fresh water | 6.60E-05 mg.l-1 | RCR = 2.20E-03 | Acceptable |
| Sediment (fresh water) | 5.47E-03 mg.kg-1 | RCR = 1.00E-02 | Acceptable |
| Agricultural soil | 1.41E-04 mg.kg-1 | RCR = 3.94E-04 | Acceptable |
| Groundwater | 2.90E-04 µg/l |  | |
| **ES 7** | SL (consumers) - GRG articles - balloons | | |
| Sewage Treatment Plant | 3.35E-04 mg.l-1 | RCR = 2.28E-04 | Acceptable |
| Fresh water | 9.90E-05 mg.l-1 | RCR = 3.30E-03 | Acceptable |
| Sediment (fresh water) | 6.07E-03 mg.kg-1 | RCR = 1.11E-02 | Acceptable |
| Agricultural soil | 9.42E-04 mg.kg-1 | RCR = 2.63E-03 | Acceptable |
| Groundwater | 1.85E-02 µg/l |  | |
| **ES 8** | IS - pre-step tyre - manufacturing and handling of DPG grad GC | | |
| Sewage Treatment Plant | 2.64E-03 mg.l-1 | RCR = 1.80E-03 | Acceptable |
| Fresh water | 3.29E-04 mg.l-1 | RCR = 1.10E-02 | Acceptable |
| Sediment (fresh water) | 1.03E-02 mg.kg-1 | RCR = 1.89E-02 | Acceptable |
| Agricultural soil | 6.53E-03 mg.kg-1 | RCR = 1.83E-02 | Acceptable |
| Groundwater | **0.15 µg/l** |  | |
| **ES 9** | IS - Manufacture of Tyres - Production and Retreading | | |
| Sewage Treatment Plant | 2.64E-03 mg.l-1 | RCR = 1.80E-03 | Acceptable |
| Fresh water | 3.29E-04 mg.l-1 | RCR = 1.10E-02 | Acceptable |
| Sediment (fresh water) | 1.03E-02 mg.kg-1 | RCR = 1.89E-02 | Acceptable |
| Agricultural soil | 6.53E-03 mg.kg-1 | RCR = 1.83E-02 | Acceptable |
| Groundwater | **0.15 µg/l** |  | |
| **ES 10** | SL (professional worker) - Garage owner - tyres change | | |
| Sewage Treatment Plant | 1.27E-03 mg.l-1 | RCR = 8.62E-04 | Acceptable |
| Fresh water | 1.92E-04 mg.l-1 | RCR = 6.40E-03 | Acceptable |
| Sediment (fresh water) | 7.78E-03 mg.kg-1 | RCR = 1.43E-02 | Acceptable |
| Agricultural soil | 3.20E-03 mg.kg-1 | RCR = 8.95E-03 | Acceptable |
| Groundwater | 7.01E-02 µg/l |  | |
| **ES 11** | SL (consumers) - Consumer use of tyres (vehicles) | | |
| Sewage Treatment Plant | 1.27E-03 mg.l-1 | RCR = 8.62E-04 | Acceptable |
| Fresh water | 1.92E-04 mg.l-1 | RCR = 6.40E-03 | Acceptable |
| Sediment (fresh water) | 7.78E-03 mg.kg-1 | RCR = 1.43E-02 | Acceptable |
| Agricultural soil | 3.20E-03 mg.kg-1 | RCR = 8.95E-03 | Acceptable |
| Groundwater | 7.01E-02 µg/l |  | |
| **ES 12** | SL (professional worker) - End of Life Tyre: ELT pre-processing storage | | |
| Sewage Treatment Plant | 3.49E-04 mg.l-1 | RCR =2.37E-04 | Acceptable |
| Fresh water | 1.00E-04 mg.l-1 | RCR = 3.34E-03 | Acceptable |
| Sediment (fresh water) | 6.10E-03 mg.kg-1 | RCR = 1.12E-02 | Acceptable |
| Agricultural soil | 9.74E-04 mg.kg-1 | RCR = 2.72E-03 | Acceptable |
| Groundwater | 1.93E-02 µg/l |  | |
| **ES 13** | F - End of Life tyre: Coarse shredding | | |
| Sewage Treatment Plant | NR | NR | NR |
| Fresh water | 6.55E-05 mg.l-1 | RCR = 2.18E-03 | Acceptable |
| Sediment (fresh water) | 5.46E-03 mg.kg-1 | RCR= 1.00E-02 | Acceptable |
| Agricultural soil | 1.28E-04 mg.kg-1 | RCR =3.58E-04 | Acceptable |
| Groundwater | 8.92E-03 µg/l |  | |
| **ES 14** | F - End of life Tyre: Grinding (ambiant) | | |
| Sewage Treatment Plant | NR | NR | NR |
| Fresh water | 6.55E-05 mg.l-1 | RCR = 2.18E-03 | Acceptable |
| Sediment (fresh water) | 5.46E-03 mg.kg-1 | RCR= 1.00E-02 | Acceptable |
| Agricultural soil | 1.28E-04 mg.kg-1 | RCR =3.58E-04 | Acceptable |
| Groundwater | 8.92E-03 µg/l |  | |
| **ES 15** | F - End of Life Tyre: Grinding cryogenic | | |
| Sewage Treatment Plant | 1.28E-03 mg.l-1 | RCR = 8.72E-04 | Acceptable |
| Fresh water | 1.94E-04 mg.l-1 | RCR = 6.52E-02 | Acceptable |
| Sediment (fresh water) | 7.81E-03 mg.kg-1 | RCR = 7.35E-02 | Acceptable |
| Agricultural soil | 3.24E-03 mg.kg-1 | RCR = 9.06E-03 | Acceptable |
| Groundwater | 7.09E-02 µg/l |  | |
| **ES 16** | F - End of Life Tyre: Pyrolysis | | |
| Sewage Treatment Plant | 3.77E-04 mg.l-1 | RCR = 2.57E-04 | Acceptable |
| Fresh water | 1.03E-04 mg.l-1 | RCR = 2.07E-02 | Acceptable |
| Sediment (fresh water) | 6.15E-03 mg.kg-1 | RCR = 2.87E-02 | Acceptable |
| Agricultural soil | 1.04E-03 mg.kg-1 | RCR = 2.92E-03 | Acceptable |
| Groundwater | 2.08E-02 µg/l |  | |
| **ES 17** | F - End of Life Tyre: Energy recovery: cement kiln | | |
| Sewage Treatment Plant | NR | NR | NR |
| Fresh water | 6.55E-05 mg.l-1 | RCR = 2.18E-03 | Acceptable |
| Sediment (fresh water) | 5.46E-03 mg.kg-1 | RCR= 1.00E-02 | Acceptable |
| Agricultural soil | 1.28E-04 mg.kg-1 | RCR =3.58E-04 | Acceptable |
| Groundwater | 8.92E-03 µg/l |  | |
| **ES 18** | F - End of Life Tyre: Energy recovery: other | | |
| Sewage Treatment Plant | NR | NR | NR |
| Fresh water | 6.55E-05 mg.l-1 | RCR = 2.18E-03 | Acceptable |
| Sediment (fresh water) | 5.46E-03 mg.kg-1 | RCR= 1.00E-02 | Acceptable |
| Agricultural soil | 1.28E-04 mg.kg-1 | RCR =3.58E-04 | Acceptable |
| Groundwater | 8.92E-03 µg/l |  | |
| **ES 19** | F - End of Life Tyre: Electric arc furnace | | |
| Sewage Treatment Plant | 6.79E-04 mg.l-1 | RCR = 4.62E-04 | Acceptable |
| Fresh water | 1.33E-04 mg.l-1 | RCR = 3.55E-02 | Acceptable |
| Sediment (fresh water) | 6.70E-03 mg.kg-1 | RCR = 4.36E-02 | Acceptable |
| Agricultural soil | 1.77E-03 mg.kg-1 | RCR = 4.96E-03 | Acceptable |
| Groundwater | 3.75E-02 µg/l |  | |
| **ES 20** | F - End of Life Tyre: Devulcanization/reclaim | | |
| Sewage Treatment Plant | 1.51E-04 mg.l-1 | RCR = 1.03E-04 | Acceptable |
| Fresh water | 8.06E-05 mg.l-1 | RCR = 2.65E-03 | Acceptable |
| Sediment (fresh water) | 5.74E-03 mg.kg-1 | RCR = 1.05E-02 | Acceptable |
| Agricultural soil | 4.94E-04 mg.kg-1 | RCR = 1.32E-03 | Acceptable |
| Groundwater | 8.34E-03 µg/l |  | |
| **ES 21** | SL (professional worker) - ELT articles - installation of shock absorbing tiles | | |
| Sewage Treatment Plant | 1.41E-04 mg.l-1 | RCR = 9.60E-05 | Acceptable |
| Fresh water | 7.96E-05 mg.l-1 | RCR = 2.65E-03 | Acceptable |
| Sediment (fresh water) | 5.72E-03 mg.kg-1 | RCR = 1.05E-02 | Acceptable |
| Agricultural soil | 4.70E-04 mg.kg-1 | RCR = 1.32E-03 | Acceptable |
| Groundwater | 7.81E-03 µg/l |  | |
| **ES 22** | SL (consumers) - ELT articles – shock absorbing tiles | | |
| Sewage Treatment Plant | 1.41E-04 mg.l-1 | RCR = 9.60E-05 | Acceptable |
| Fresh water | 7.96E-05 mg.l-1 | RCR = 2.65E-03 | Acceptable |
| Sediment (fresh water) | 5.72E-03 mg.kg-1 | RCR = 1.05E-02 | Acceptable |
| Agricultural soil | 4.70E-04 mg.kg-1 | RCR = 1.32E-03 | Acceptable |
| Groundwater | 7.81E-03 µg/l |  | |
| **ES 23** | SL (professional worker) – re-use of ELT articles - installation of synthetic turf fields | | |
| Sewage Treatment Plant | 1.41E-04 mg.l-1 | RCR = 9.60E-05 | Acceptable |
| Fresh water | 7.96E-05 mg.l-1 | RCR = 2.65E-03 | Acceptable |
| Sediment (fresh water) | 5.72E-03 mg.kg-1 | RCR = 1.05E-02 | Acceptable |
| Agricultural soil | 4.70E-04 mg.kg-1 | RCR = 1.32E-03 | Acceptable |
| Groundwater | 7.81E-03 µg/l |  | |
| **ES 24** | SL (consumers) - ELT articles – synthetic turf fields | | |
| Sewage Treatment Plant | 1.41E-04 mg.l-1 | RCR = 9.60E-05 | Acceptable |
| Fresh water | 7.96E-05 mg.l-1 | RCR = 2.65E-03 | Acceptable |
| Sediment (fresh water) | 5.72E-03 mg.kg-1 | RCR = 1.05E-02 | Acceptable |
| Agricultural soil | 4.70E-04 mg.kg-1 | RCR = 1.32E-03 | Acceptable |
| Groundwater | 7.81E-03 µg/l |  | |

NR: not relevant, M: Manufacture, F: Formulation, IS: Industrial site, SL: Service Life

REGIONAL assessment

The exposure estimates have been carried out by the Registrants and aMSCA’s is in agreement with the conclusions to consider the impact of the regional scale as negligible on environmental assessment.

Conclusion for environment

Based on the exposure scenarios of the registration dossier, environmental risk assessment shows **unacceptable risks for exposure to fresh water and sediment in scenario 1a** (Manufacture of the substance – Registrant 1) **following direct release of the substance to the water**. This conclusion differ from the registrant. The aMSCA revised the flow rate of the river and the dilution factor which were found to be inaccurate. This corrected value has a major impact on the dilution of DPG in the water course and the overall risk calculation.

Environmental risk assessment shows **unacceptable risks for exposure to agricultural soil in scenario 1b** (Manufacture of the substance - Registrant 2) following effluent treatment in the sewage treatment plant located on the site of the manufacture. Release to groundwater was also identified. However, the registrant mentioned that no application of the STP sludge is made on agricultural soil and that particular considerations are made on the waste treatment operations. Thus, **the aMSCA considers the risks acceptable following the application of appropriate risk management measure (no application of sludge to agricultural soil)**.

Environmental risk assessment shows **unacceptable risks for scenarios 2, 3 and 4 for fresh water and sediments following direct release of the substance to the water**. In these scenarios, the Registrants mentioned that there is no DPG-containing wastewater in this process. The aMSCA considers the zero emission as an unrealistic emission scenario and applied the release to wastewater relevant for each corresponding ERCs as a default value and following the recommendations of R.16 Guidance document. Additional information was given from one of the two manufacturers for scenario 2 (F - Formulation or re-packing – Masterbatches manufacture - Mixland). In the confidential document submitted (personal communication to the aMSCA), the registrant gives details on the processes of formulation, the operators’ duties, the cleaning and waste management. It is mentioned that the bags used for packaging, the floor and equipment are not washed with water. The waste (bags) is monitored using a BSD – “Bordereau suivi des déchets” as mandatory by the French regulation. The mixing tank cleaning is done dry or scraping with rags soaked in solvent, there is no cleaning with water installation. The extruder is cooled with cold water (the cooling system is tight and there is no contact with the product). These measures, if applied correctly, allow to reduce efficiently the release of DPG in the environment. Thus, **the aMSCA considers the risks acceptable following the application of appropriate risk management measures as detailed by one of the registrants. These specific management measures shall be included in the registration dossier. There is however uncertainty whether such management measures are applied by all registrants. A more detailed description of the operational conditions and monitoring data should be provided by all registrants concerned with scenarios 2, 3 and 4 to discard the risks identified in this assessment.**

**In addition, monitoring the aquatic environment at the local scale, in the vicinity of the releases of DPG from industrial sites, would provide relevant information to discard uncertainties in relation to risk assessment. This would apply to scenario 1a** (Manufacture of the substance – Registrant 1) and to scenario 2, 3, 4 (Formulation or re-packing scenarios)**, to cover the uncertainties related to the surface water flow of the river receiving the industrial wastewater. This could also apply to scenarios 8 and 9** (Manufacture of Tyres) **for which both scenarios indicated a predicted exposure concentration of DPG to groundwater of 0.15 µg/L.**

## Overall risk characterisation

**Human health (combined for all exposure routes)**

**In conclusion, when considering all the exposure scenarios presented in the CSRs and the revised DNELs recommended by the aMSCA, some RCR are between >1 and 1.61:**

* **most scenarios for industrial workers and several scenarios for professional workers**
* **change of new tyres by consumers (RCR =1.13)**

It has to be noted that in most of the exposure scenario (except for scenario 1a and 1b), only a Tier I assessment tool was used. Moreover, dermal route is identified as a significant route of exposure in many of the exposure scenario in which RCR were greater than 1 and the RMMs did not systematically include glove wearing. Gloves may be added to lower the risks. Additional operational conditions (OCs) and RMMs may be also implemented. However, it is noted that implementation and compliance to additional OCs and RMMs may be more difficult to achieve in professional situations than in industrial installation.

**Considering the low magnitude of risks, refinement of exposure assessment with Tier II tools and addition of RMM may result in refinement and possibly control of risks. The aMSCA therefore recommend that registration dossiers above 10 Tpa are updated considering the DNEL as described in section 2.1.1 to provide demonstration that risks are adequately controlled for all registered uses of the substance.** It is possible that despite a refinement and the addition of OCs and RMMs, risks remain. It is however not possible for the aMSCA to go further in the analysis.

**Besides, in addition to the information given in the CSR, data from the literature provided indications of sources of exposure to DPG.** Contact allergy due to the presence of DPG in gloves, shoes and sock is reported. DPG was detected in drinking water and sources of drinking water in several publications. DPG was also detected in indoor dust and in the air of megacities in countries across the word. It can be noted the DPG concentrations varied a lot between the publications. This may be explained by the differences of sensitivity of detection methods. Other parameters may also have influence but are not known. The identified and possible sources includes release from tire particles, from use of rubber goods and in particular from water pipes for drinking water. One publication also report the contamination of pharmaceutical products by DPG coming from the material used to manipulate the drug.

Risk calculation were performed with the concentrations of DPG in water (drinking water and sources of drinking water) from 3 publications. Risks were determined for infants, children and adults for the concentration of 560µg/L of DPG in drinking water (Tang *et al*. 2015). The origin of DPG in this publication is from migration from HDPE pipes material. This type of pipe is also used in Europe (Diera *et al*. 2023). However, it is difficult to know if the material composition is the same in China than in Europe. Therefore, it is not known whether the concentration reported in the publication of Tang *et al*. (2015) is representative of the DPG concentration in drinking water in Europe.

Nevertheless, a potential risk due to the presence of DPG in drinking water cannot be dismissed.

Overall, DPG has been detected in many sources other than those covered by the exposure scenario of the CSRs and the extent of the articles where DPG is present is not known. **This raise uncertainties on the representativeness of the exposure scenarios presented in the CSR regarding the possible extent of the articles in which DPG is present. There are also uncertainties on the residual amount of DPG present in articles. No data was found in the literature.**

The exposure of DPG to the general population is therefore from multiple sources and appears to be continuous.

A classification as Repr. 1B – H360FD is proposed by aMSCA. The presence of DPG in many sources raise concern.

**Environment (combined for all exposure routes)**

The main concern related to the exposure and the risk for the environment is due to the direct release of the substance to surface water during the manufacture of DPG at industrial sites. Manufacture exposure scenario from one of the 2 manufacturers predicted unacceptable risks to surface water and sediments. In addition, risks were identified during formulation steps. These risks could be covered following the application of appropriate risk management measures as detailed by one of the registrants. There is however uncertainty whether such management measures are applied by all registrants and these management measures should be clearly indicated in the chemical safety report of each relevant registrant.

After consideration of the risks identified, and in the absence of data mentioning the concentration of the substance in the water course, the aMSCA is of the opinion that measurements and monitoring of release of DPG into surface water are necessary to confirm that appropriate risk management measures are effective in limiting the emission of DPG in the environment to a safe level.

Exposure scenarios as developed by the registrants are limited to the manufacture and formulation of DPG, and consider a limited amount of manufactured articles. Uncertainties remain regarding additional exposure scenarios that might cover the diversity of articles containing DPG, give information on the concentration of DPG in articles and take into account the release of DPG during the service life of articles (leaching). The exposure and risks related to tyres abrasion and release of DPG in the aquatic environment is of concern. Monitoring information showed that DPG is a ubiquitous substance and literature indicate that tyres abrasion could be a major source of DPG release in the environment. However, the exposure scenarios as provided in the registration dossier do not reflect the exposition of the substance to the aquatic environment as found in the literature and the risk associated to tyres abrasion or leaching from other rubber articles.

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