Screening Assessment for the Challenge

Guanidine, *N*,*N*'-diphenyl-

(Diphenylguanidine)

Chemical Abstracts Service Registry Number
102-06-7

Environment Canada
Health Canada

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Synopsis

Pursuant to section 74 of the *Canadian Environmental Protection Act, 1999* (CEPA 1999), the Ministers of the Environment and of Health have conducted a screening assessment of Guanidine, *N,N'*-diphenyl-, commonly referred to as diphenylguanidine or DPG, Chemical Abstracts Service Registry Number[1] 102-06-7. DPG was identified as a high priority for screening assessment and included in the Challenge initiative under the Chemicals Management Plan because it was considered to pose an intermediate potential for exposure of individuals in Canada and had been classified by other agencies on the basis of reproductive toxicity. This substance met the ecological criteria for persistence, but not for bioaccumulation potential and inherent toxicity to aquatic organisms.

DPG does not occur naturally in the environment. According to information received under section 71 of CEPA 1999, no companies reported manufacturing DPG in Canada in 2006, but 100 000 – 1 000 000 kg of DPG was imported into Canada and 100 000 – 1 000 000 kg of DPG was used. Less than 100 kg of DPG was reported to be released to air, and, similarly, less than 100 kg of the substance was reported to be released to water in Canada in 2006. DPG is primarily used as an accelerator to achieve shorter curing times during the vulcanization process in the manufacture of rubber for tires and industrial applications. According to data submitted under section 71 of CEPA 1999, DPG is used in the manufacture of rubber tires, rubber mixtures, industrial rubber sheets, and sealants for automotive and navy applications in Canada.

Based on the available information, exposure to DPG among the general population in Canada through environmental media (except soil) is considered to be negligible. Exposure to DPG from dietary sources is not expected. According to the information available and industry data reported under section 71 of CEPA 1999, DPG is used in Canada to manufacture rubber material for tires and industrial applications. Exposure to DPG via soil containing tire debris was estimated and found to be low. Exposure of the general population from consumer products is not expected.

The critical health effect associated with exposure to DPG is reproductive toxicity, based on the observations in experimental animals and the weight of evidence-based classification by other international agencies.

The margin between upper bound estimates of exposure of the general population to DPG via contact with soil containing tire debris and the lowest effect level in experimental animals is considered adequate to address uncertainties in the health effects and exposure databases.

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Based on the information available, it is concluded that DPG does not meet the criteria under paragraph 64*(c)* of CEPA 1999, as it is not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

Based on available empirical and modelled data, DPG meets the criteria for persistence, but not for bioaccumulation potential, as set out in the *Persistence and Bioaccumulation Regulations*. It is expected to have a moderate potential for toxicity to aquatic organisms, with highest potential for toxicity to certain species of algae. A risk quotient analysis, integrating conservative estimates of exposure with toxicity information, was performed for the aquatic medium to determine whether there is potential for ecological harm in Canada. The risk quotients indicated that the current estimated site-specific industrial exposure concentrations of DPG in water are unlikely to cause harm to aquatic organisms. Based on this information, it is concluded that DPG does not meet the criteria in paragraphs 64*(a)* and *(b)* of CEPA 1999, as it is not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity or that constitute or may constitute a danger to the environment on which life depends.

Based on the information available, it is concluded that DPG does not meet any of the criteria set out in section 64 of the Canadian Environmental Protection Act, 1999.

This substance will be considered for inclusion in the Domestic Substances List inventory update initiative. In addition and where relevant, research and monitoring will support verification of assumptions used during the screening assessment.

Introduction

The *Canadian Environmental Protection Act, 1999* (CEPA 1999) (Canada 1999) requires the Minister of the Environment and the Minister of Health to conduct screening assessments of substances that have met the categorization criteria set out in the Act to determine whether these substances present or may present a risk to the environment or to human health.

Based on the information obtained through the categorization process, the Ministers identified a number of substances as high priorities for action. These include substances that

- met all of the ecological categorization criteria, including persistence (P), bioaccumulation potential (B) and inherent toxicity to aquatic organisms (iT), and were believed to be in commerce in Canada; and/or
- met the categorization criteria for greatest potential for exposure (GPE) or presented an intermediate potential for exposure (IPE) and had been identified as posing a high hazard to human health based on classifications by other national or international agencies for carcinogenicity, genotoxicity, developmental toxicity or reproductive toxicity.

The Ministers therefore published a notice of intent in the *Canada Gazette*, Part I, on December 9, 2006 (Canada 2006), which challenged industry and other interested stakeholders to submit, within specified timelines, specific information that may be used to inform risk assessment and to develop and benchmark best practices for the risk management and product stewardship of those substances identified as high priorities.

The substance Guanidine, *N*,*N*'-diphenyl- (DPG) was identified as a high priority for assessment of human health risk because it was considered to present an IPE and had been classified by other agencies on the basis of reproductive toxicity.

The Challenge for DPG was published in the *Canada Gazette* on December 26, 2009 (Canada 2009). A substance profile was released at the same time. The substance profile presented the technical information available prior to December 2005 that formed the basis for categorization of this substance. As a result of the Challenge, submissions of information pertaining to the substance were received.

Although DPG was determined to be a high priority for assessment with respect to human health and to meet the ecological categorization criteria for persistence, it did not meet the criteria for bioaccumulation potential or inherent toxicity to aquatic organisms. Therefore, this assessment focuses principally on information relevant to the evaluation of risks to human health.

Screening assessments focus on information critical to determining whether a substance meets the criteria as set out in section 64 of CEPA 1999. Screening assessments examine

scientific information and develop conclusions by incorporating a weight of evidence approach and precaution.[2]

This final screening assessment includes consideration of information on chemical properties, hazards, uses and exposure, including the additional information submitted under the Challenge. Data relevant to the screening assessment of this substance were identified in original literature, review and assessment documents and stakeholder research reports and from recent literature searches, up to August 2010 for ecological effects and May 2010 for human health effects and exposure. Key studies were critically evaluated; modelling results may have been used to reach conclusions.

Evaluation of risk to human health involves consideration of data relevant to estimation of (non-occupational) exposure of the general population, as well as information on health hazards (based principally on the weight of evidence assessments of other agencies that were used for prioritization of the substance). Decisions for human health are based on the nature of the critical effect and/or margins between conservative effect levels and estimates of exposure, taking into account confidence in the completeness of the identified databases on both exposure and effects, within a screening context. The final screening assessment does not represent an exhaustive or critical review of all available data. Rather, it presents a summary of the existing critical information upon which the conclusion is based.

This final screening assessment was prepared by staff in the existing substances programs at Health Canada and Environment Canada and incorporates input from other programs within these departments. The ecological and human health portions of this assessment have undergone external written peer review/consultation. Comments on the technical portions relevant to human health were received from Dr. Irene Abraham, Toxicology Excellence for Risk Assessment; Dr. Michael Jayjock, The LifeLine Group; and Dr. Susan Griffin, U.S. EPA. Approaches used in screening assessments under the Challenge have been reviewed by an independent Challenge Advisory Panel. Although external comments were taken into consideration, the final content and outcome of the final screening assessment remain the responsibility of Health Canada and Environment Canada.

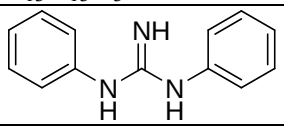
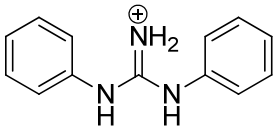
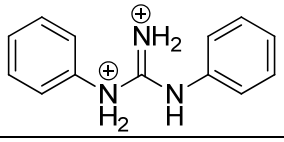
The critical information and considerations upon which the final assessment is based are summarized below.

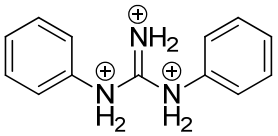
[2] A determination of whether one or more of the criteria of section 64 are met is based upon an assessment of potential risks to the environment and/or to human health associated with exposures in the general environment. For humans, this includes, but is not limited to, exposures from ambient and indoor air, drinking water, foodstuffs, and the use of consumer products. A conclusion under CEPA 1999 on the substances in the Chemicals Management Plan (CMP) Challenge Batches 1-12 is not relevant to, nor does it preclude, an assessment against the hazard criteria specified in the Controlled Products Regulations, which is part of regulatory framework for the Workplace Hazardous Materials Information System [WHMIS] for products intended for workplace use. Similarily, a conclusion based on the criteria contained in section 64 of CEPA 1999 does not preclude actions being taken under other sections of CEPA or other Acts.

Substance Identity

For the purposes of this document, Guanidine, *N*,*N*'-diphenyl-, will be referred to as DPG, derived from the common name Diphenylguanidine. Information on the identity of DPG is summarized in Table 1.

Table 1. Substance identity for DPG

Chemical Abstracts Service Registry Number (CAS RN)	**102-06-7**
DSL name	**Guanidine, *N*,*N*'-diphenyl-**
National Chemical Inventories (NCI) names [1]	*Guanidine, N,N'-diphenyl- (TSCA, PICCS, ASIA-PAC, NZIoC);* *1,3-diphenylguanidine (EINECS, ENCS, ECL);* *diphenylguanidine (ENCS, PICCS);* *diphenyl guanidine (PICCS);* *guanidine, N,N'-diphenyl- (AICS, SWISS);* *N,N'-diphenyl guanidine (PICCS);* *guanidine, 1,3-diphenyl (PICCS);* *DPG (Vulcacit D) (PICCS)*
Other names	*1,2-Diphenylguanidine; Accel D; Accel DM-R; Accelerator D; Chlorostain;BR; Denax; Denax DPG; DFG; DPG; Melaniline; N,N-Diphenylguanidine; Nocceler D; NSC 3272; Perkacit DP; Perkacit DPG; Rhenogran DPG; Rhenogran DPG 80; Rhenogran DPG 80P; Sanceler D; Sanceler D-G; Soxinol D; Soxinol DG; sym-Diphenylguanidine; Vanax; DPG; Vulcafor DPG; Vulkacit D; Vulkacit D/C; Vulkazit*
Chemical group (DSL Stream)	Discrete organics
Major chemical class or use	Complex aromatic amine
Major chemical sub-class	Guanidine derivatives (phenyls)
Chemical formula	$C_{13}H_{13}N_3$
Chemical structure (neutral form: DPG)	
Chemical structure (ionic form: DPG-H^+)	
Chemical structure (ionic form: DGP-H_2^{2+})	

Chemical structure (ionic form: DGP-H_3^{3+}**)**	
SMILES (neutral form) [2]	N=C(Nc(cccc1)c1)Nc(cccc2)c2
Molecular mass (neutral form)	211.27 g/mol

[1] National Chemical Inventories (NCI). 2009: AICS (Australian Inventory of Chemical Substances); ASIA-PAC (Asia-Pacific Substances Lists); ECL (Korean Existing Chemicals List); EINECS (European Inventory of Existing Commercial Chemical Substances); ENCS (Japanese Existing and New Chemical Substances); NZIoC (New Zealand Inventory of Chemicals);PICCS (Philippine Inventory of Chemicals and Chemical Substances); SWISS-(Giftliste 1 and Inventory of Notified New Substances), and TSCA (U.S. Toxic Substances Control Act Chemical Substance Inventory).

[2] Simplified Molecular Input Line Entry System

Impurities that have been reported in the commercial product are aniline and nitrogenous polymers, both in concentrations less than 1% (OECD 2002).

The substance, denoted as DPG, is expected to protonate significantly in water at common ambient pH so that the main form present in water is the ionic form DPG-H^+ as shown above in Table 1 and explained below.

According to the modelling program pKaDB from ACD/pKaDB (2005), the substance ionizes in water as a base in three steps, by attracting one proton to each of the amine groups. Using DPG to denote the neutral form of the substance, its ionization steps and acid dissociation constants are predicted by the program as follows:

DPG-H^+	↔	DPG + H^+	pKa1 = 10.12
DGP-H_2^{2+}	↔	DPG-H^+ + H^+	pKa2 = -1.08
DPG-H_3^{3+}	↔	DPG-H_2^{2+} + H^+	pKa3 = -8.16

The general ionization can be represented by the equation:

Acid ↔ Conjugate Base + H^+ Ka = [Conjugate Base][H^+]/[Acid]

Under a given pH, the acid-to-base concentration ratio is given as

$$[\text{Acid}]/[\text{Base}] = 10^{\text{pKa-pH}}$$

The primary acid dissociation constant (pKa1 = 10.12) is greater than 9, which indicates that there is nearly complete protonation of the substance forming DPG-H^+ in this first step under environmental conditions. Therefore the neutral form – DPG - is at comparatively much lower concentrations in aqueous solution. The secondary acid dissociation constant (pKa2 = -1.08) is well below 5, which indicates that the protonation of DPG-H^+ in this step is negligible, therefore, the DPG-H^+ will be present in water in much greater proportion than DPG-H_2^{2+} (Table 2). Finally, the tertiary acid dissociation

constant (pKa3 = -8.16) is also much smaller than 5, which indicates that there is no further protonation of DPG-H_2^{2+}, such that DPG-H_3^{3+} will only be present in water at comparatively much lower concentrations than DPG-H^+.

In summary, the substance DPG significantly protonates in water, such that the predominant form present in natural waters is the ionized form DPG-H^+. The proportion of the forms in water is calculated by dividing its relative concentration by the total under a given pH using the above acid base equation, as summarized in Table 2 (Environment Canada 2010a).

Table 2. Proportions of different forms of DPG in water at various pH values

pH	Proportion (%)				
	DPG	**DPG-H^+**	**DPG-H_2^{2+}**	**DPG-H_3^{3+}**	Total
5.0	0.0	100.0	0.0	0.0	100.0
6.0	0.0	100.0	0.0	0.0	100.0
7.0	0.1	99.9	0.0	0.0	100.0
8.0	0.8	99.2	0.0	0.0	100.0
9.0	7.1	92.9	0.0	0.0	100.0

Physical and Chemical Properties

Table 3 below contains experimental and modelled physical and chemical properties of DPG that are relevant to its environmental fate.

Table 3. Physical and chemical properties for the neutral form (unless noted otherwise) of DPG.

Property	Type	Value[1]	Temperature (°C)	Reference
Melting point (ºC)	Experimental	150 *		Howard 1989; PhysProp 2006
	Modelled	120.14		MPBPWIN 2008
Boiling point (ºC)	Modelled	360.5 **		MPBPWIN 2008
Vapour pressure (Pa)	Modelled	5.29×10^{-4} (3.97×10^{-6} mm Hg)		MPBPWIN 2008

Property	Type	Value[1]	Temperature (°C)	Reference
Henry's Law constant ($Pa \cdot m^3/mol$)	Modelled	1.12×10^{-4} (1.1×10^{-9} atm · m^3/mol)	25	HENRYWIN 2008
Log K_{ow} (log of the octanol-water partition co-efficient (dimen-sionless))	Modelled	2.89		EPIsuite 2008
Log D *** (log of the octanol-water partition co-efficient for ionic species (dimension-less))	Modelled (accounting for charged form)	0.73 (at pH 5)		ACD/pKaDB 2005
		2.13 (at pH 7)		
		2.36 (at pH 9)		
Log K_{oc} (log of the organic carbon-water partition coefficient) (dimensionless))	Modelled	3.22		KOCWIN 2008 (MCI method)
	Modelled	2.44		KOCWIN 2008 (log Kow method)
Log K_{oa} (log of the organic carbon-air partition coefficient (dimen-sionless))	Modelled	12.43		KOAWIN 2008
Water solubility (mg/L)	Experimental (accounting for charged form)	1000 *	25	MITI 1992
	Modelled	68.83	25	WATERNT 2008
pK_a (acid dissociation constant) (dimen-	Experimental	10.12 (pK_a1) -1.08 (pK_a2) -8.16 (pK_a3)		Perrin 1965

Property	Type	Value[1]	Temperature (°C)	Reference
sionless))				

[1] Values in parentheses represent the original ones as reported by the authors or as estimated by the models
* indicates selected value for modelling
** According to the Merck Index, DPG decomposes at 170 deg C.
*** Log D is the distribution coefficient taking into account the presence of the ionic species; it represents a net amount of the neutral and ionic forms expected to partition into the lipid or organic carbon phases at a given pH.

Sources

DPG is an anthropogenic substance and does not occur naturally in the environment. It can be prepared by reacting aniline and chlorine cyanide at 160°C in a molar ratio of 2:1 (GDCh-BUA 1992). According to data submitted in response to a section 71 survey notice of CEPA 1999, no companies in Canada reported manufacturing DPG in a quantity greater than or equal to the reporting threshold of 100 kg in 2006. However, it was reported that this substance was imported into Canada in the range of 100 000–1 000 000 kg in the same year (Environment Canada 2010b). During the 1986 calendar year, it was reported that approximately 100 000–1 000 000 kg of DPG was manufactured, imported or in commerce in Canada (Environment Canada 1988).

Uses

According to data submitted under a section 71 survey notice of CEPA 1999, DPG is used in the manufacture of rubber tires, rubber mixtures, industrial rubber sheets, and sealants for automotive and navy applications in Canada (Environment Canada 2010b). Based on the available information, DPG is used in Canada to manufacture rubber material for tires and industrial applications (Environment Canada 2010b; May 2010 email from Risk Management Bureau, Health Canada to Existing Substances Division, Health Canada; unreferenced). The total use quantity of DPG in Canada reported under section 71 for the year 2006 was in the range of 100 000–1 000 000 kg (Environment Canada 2010b).

Globally, DPG is used as an accelerator to achieve shorter curing times in the vulcanization process to manufacture rubber for products such as tires, footwear, rubber gloves, cable, hoses and moulded goods (Ross 1969; IARC 1982; Feinman 1987; GDCh-BUA 1992; NTP 1995; Ohm 2000). DPG (approximately 1 tonne) was reported to also be used in "special papers" (e.g., forgery-proof filing paper) in 1991 in Germany (GDCh-BUA 1992).

DPG is not listed as an approved food additive under Division 16 of the *Food and Drug Regulations* (Canada 1978) and has never been used in incidental additives products in

Canada (2010 personal communication from Food Directorate, Health Canada, to Risk Management Bureau, Health Canada; unreferenced).The U.S. Food and Drug Administration lists DPG as an indirect additive used in food contact rubber articles intended for repeated use (US FDA 2008). A similar use of DPG in coffee siphon packaging was reported in Japan (Baba 1980). DPG is listed in the Natural Health Products Ingredient Database (NHPID) as a Non-NHP substance and not found in the Licensed Natural Health Products Database (LNHPD), as a medicinal or non-medicinal ingredient present in licensed natural health products in Canada (NHPID 2011; LNHPD 2011).

DPG is currently listed in the Drug Products Database (DPD) as a medicinal ingredient in an allergy patch test for humans (DPD 2010). Since allergy tests are conducted infrequently and the amount of DPG is only 0.068 mg per patch, the allergy patch is not considered a significant source of exposure to the general population (DPD 2010; 2010 personal communications from Therapeutic Products Directorate, Health Canada, to Risk Management Bureau, Health Canada; unreferenced). DPG is not listed in the Therapeutic Products Directorate's internal Non-Medicinal Ingredients Database as a non-medicinal ingredient in pharmaceuticals and is not expected to be present in veterinary drugs (2010 personal communication from Therapeutic Products Directorate & Veterinary Drugs Directorate, Health Canada, to Risk Management Bureau, Health Canada; unreferenced).

The use of DPG as a tracer/dye (non-active ingredient) in six pesticide products is regulated in Canada under the Pest Control Products Act (Canada 2002). All six products are classified as "restricted" (only for use by certified applicators) and thus are not available for use by the general public (September 2010 email from Pest Management Regulatory Agency, Health Canada, to Existing Substances Division, Health Canada; unreferenced). DPG is not registered as an active ingredient (PMRA 2010).

DPG is not listed in Health Canada's Cosmetic Notification System (CNS 2010). Furthermore it is not included in Health Canada's Cosmetic Ingredient Hotlist, an administrative list of ingredients that are intended to be prohibited or restricted for use in cosmetics in Canada (Health Canada 2007). It is not expected that DPG would be present in registered cosmetic products in Canada.

Releases to the Environment

In response to a notice issued under section 71 of CEPA 1999, less than 100 kg of DPG was reported to be released to air, and similarly, less than 100 kg of the substance was reported to be released to water in Canada in 2006. Less than 100 kg and between 1 000–10 000 kg of DPG were reported as hazardous and non-hazardous wastes, respectively, that were transferred to off-site waste management in 2006 (Environment Canada 2010b). DPG does not appear on either the National Pollutant Release Inventory (NPRI) substance list (Environment Canada 2010c) or the US Toxics Release Inventory Program list of reportable substances (TRI 2006). Its dispersive use pattern suggests possible release from wastewater treatment plants (WWTPs) and landfills.

As an accelerator predominantly used in the vulcanization process of rubber tire manufacturing, DPG may exist in the environment bound within tire wear particles as a result of abrasion of tires on roads (GDCh-BUA 1992), however no report of DPG in airborne particulate matter in Canada or elsewhere was identified.

Environmental Fate

DPG is characterized by moderate to high water solubility (1000 mg/L), low log D_{ow} (2.13 at pH 7), low to moderate log K_{oc} values (2.44 and 3.22), and low vapour pressure (5.29×10^{-4} Pa). Based on the physical and chemical properties (Table 3) and the potential uses of DPG, the substance, if released into the environment, would be expected to be ultimately found mainly in water or soil.

Given its acid dissociation constant (pK_a), most of any DPG released to water bodies with environmentally relevant pHs (5-9) will be present in the cationic form. The ionization state of a compound is important for determining its fate. The ionized form of a substance is more water-soluble than the neutral form, and will have reduced partitioning to organic phases, such as lipids and other organic matter. However, ionized substances may interact with counter-charged substrates in sediment or soil, and therefore, may have a higher partitioning to sediment or soil than would be indicated by their water solubility, log D_{ow} and log K_{oc}. The exact extent of these interactions is unknown.

If released to water, DPG is expected to largely remain in water due to its moderately high water solubility (1000 mg/L). The low to moderate estimated log D_{ow} and log K_{oc} values indicate that DPG may adsorb, to some extent, to suspended solids and sediment. In addition, DPG will exist predominantly as a cation at environmental pHs, so it may adsorb strongly to negatively charged sediment material. Volatilization from water surfaces is expected to be a relatively unimportant fate process based on this compound's estimated Henry's Law constant. Also, due to its ionized state in water at ambient pHs, it will be held in the water or soil-water by interactions with oppositely charged counterions, as well as hydrogen bonds. Thus, if water is the receiving medium, DPG is expected to largely remain in water and will be transported, to some extent, to sediment.

If released to soil, DPG may remain in soil. Volatilization from moist soil surfaces seems to be an unimportant fate process based on its very low estimated vapour pressure and Henry's Law constant. DPG is essentially non-volatile so volatilization from dry soil surfaces is not expected to be significant. Although soil runoff can result in the transfer of a certain proportion of DPG to surface water, the amount transferred would be relatively small as the runoff represents only a very small fraction of the entire soil. Therefore, if released to soil, DPG will mainly remain in this environmental compartment.

Based on the low modelled vapour pressure value of 5.29×10^{-4} Pa, DPG is considered to have low volatility. When released to air, DPG is expected to end up in soil or surface

water via wet deposition. Due to its moderate to high water solubility and moderate melting point (150ºC), atmospheric DPG would be captured in snow or rain during precipitation. As the surface area of soil is much larger than surface water for a given region, the DPG released to air would mainly transfer to soil and remain there.

If DPG is used in rubber products, or for any other use that generates solid wastes, it will end up in landfill sites through waste disposal. DPG would tend to remain, to a significant degree, in the landfill sites, since it is normally fixed into the matrices of the solid waste materials with limited contact with leachate or air.

Persistence and Bioaccumulation Potential

Environmental Persistence

Table 4a presents the empirical biodegradation data for DPG. A study shows no biodegradation over 28 days in a ready-biodegradation test for DPG (CHRIP 2008). This test indicates that the ultimate biodegradation half-life in water is likely to be longer than 182 days (6 months) and that the substance is therefore likely to persist in that environmental compartment. However, in tests using pre-adapted inoculum and unadapted river water (Bayer 1990 and Chou et al. 1980, respectively), rapid degradation was found, indicating that DPG is inherently biodegradable. Using the first-order kinetic rate equation, an ultimate degradation half-life for DPG in water of 13.6 days is calculated, assuming 76% degradation in 28 days.

Table 4a. Empirical data for degradation of DPG

Medium	Fate process	Degradation value	Degradation endpoint / units	Reference
Water	Biodegradation (ready)	0	% BOD (28 days)	CHRIP 2008
Water	Biodegradation (inherent)[1]	76	% BOD (28 days)	Bayer 1990
Water	Biodegradation (primary)	100	% Loss of substance (14 days at pH 7.5)	Chou et al. 1980
Water	Hydrolysis (80°C, pH 3.5, 500 hours)	0	%	Wohlfahrt & Niebergahl 1984
Water	Hydrolysis (80°C, pH 7.0, 1000 hours)	18.1	%	Wohlfahrt & Niebergahl 1984
Water	Hydrolysis (80°C, pH 10.5, 168 hours)	50	%	Wohlfahrt & Niebergahl 1984

[1] Using adapted sludge

Since few experimental data on the degradation of DPG are available, a quantitative structure-activity relationship (QSAR) based weight-of-evidence approach (Environment Canada 2007) was also applied using the degradation models shown in Table 4b below. Given the ecological importance of the water compartment, the fact that most of the available models apply to water and the fact that DPG is expected to be released to this compartment, primarily biodegradation in water was examined. Experimental studies indicate that DPG undergoes hydrolysis at elevated temperatures and pH (Wohlfahrt and Niebergahl 1984), but it should be noted that these temperatures are not environmentally relevant. The US EPA has estimated that hydrolysis is negligible at environmentally relevant temperatures (US EPA 2009).

Table 4b summarizes the results of available QSAR models for degradation in various environmental media.

Table 4b. Modelled data for degradation of DPG

Fate process	Model and model basis	Model result and prediction	Extrapolated half-life (days OR hours)
AIR			
Atmospheric oxidation	AOPWIN 2008[1]	$t_{1/2}$ = 0.3 days	<2
Ozone reaction	AOPWIN 2008[1]	n/a[2]	n/a
WATER			
Hydrolysis	HYDROWIN 2008[1]	n/a[2]	n/a
Primary biodegradation [3]			
Biodegradation (aerobic)	BIOWIN 2008[1] Sub-model 4: Expert Survey (qualitative results)	3.34[4] "biodegrades fast"	<182
Ultimate biodegradation			
Biodegradation (aerobic)	BIOWIN 2008[1] Sub-model 3: Expert Survey (qualitative results)	2.51[4] "biodegrades moderately fast"	< 182
Biodegradation (aerobic)	BIOWIN 2008[1] Sub-model 5: MITI linear probability	-0.15[4] "biodegrades slowly"	≥ 182
Biodegradation (aerobic)	BIOWIN 2008[1] Sub-model 6: MITI non-linear probability	0.008[5] "biodegrades slowly"	≥ 182
Biodegradation (aerobic)	TOPKAT 2004 Probability	0[5] "biodegrades slowly	≥ 182
Biodegradation (aerobic)	CPOPs 2008 % BOD (biological oxygen demand)	% BOD = 0.75 "biodegrades very slowly"	≥ 182

[1] EPIsuite (2008)
[2] Model does not provide an estimate for this type of structure.
[3] This result is interpreted from the perspective of ultimate degradation and without knowledge of the biodegradation products.
[4] Output is a numerical score from 0 to 5.
[5] Output is a probability score.

In air, a predicted atmospheric oxidation half-life value of 0.3 days (see Table 4b) demonstrates that this substance is likely to be rapidly oxidized. The substance is not

expected to react with other photo-oxidative species in the atmosphere, such as O_3, nor is it likely to degrade via direct photolysis. Therefore, it is expected that reactions with hydroxyl radicals will be the most important fate process in the atmosphere for DPG. With a half-life of 0.3 days via reactions with hydroxyl radicals, DPG is considered not persistent in air.

Results for two of the BIOWIN ultimate biodegradation models (BIOWIN Sub-models 5 and 6) indicate that biodegradation is slow and that the half-life in water is ≥ 182 days. The result for BIOWIN Sub-model 3 on the other hand suggests that ultimate degradation could be relatively fast (i.e., half-life < 182 days). The result from BIOWIN Sub-model 4 indicates that primary biodegradation is likely to be fast, but the identities of the degradation products resulting from primary degradation are not known. In addition, the ultimate degradation predictions from TOPKAT and CPOPs indicate a very slow rate of biodegradation. Also, DPG contains structural features associated with chemicals that are not easily biodegraded (e.g., aromatic amine). Therefore, considering all of the empirical and model results and structural features, there is reliable evidence to indicate that the ultimate biodegradation half-life of DPG is ≥ 182 days in water.

Using an extrapolation ratio of 1:1:4 for water: soil: sediment biodegradation half-lives (Boethling et al. 1995), the ultimate biodegradation half-life in soil is also ≥ 182 days and the half-life in sediments is ≥ 365 days. This indicates that DPG is expected to be persistent in soil and sediment.

Based on the empirical and modelled data (see Tables 4a and 4b) DPG meets the persistence criteria in water, soil, and sediment (half-lives in soil and water ≥ 182 days and half-life in sediment ≥ 365 days) as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

DPG does not meet the criteria for air (half-life in air ≥ 2 days) as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

Potential for Bioaccumulation

The experimental and modelled log D_{ow} and log K_{ow} values for DPG indicate that this chemical has a relatively low potential to bioaccumulate in biota (see Table 3).

Table 5a presents the empirical bioconcentration factor (BCF) values in fish.

Table 5a. Empirical data for bioaccumulation of DPG

Test organism	Endpoint	Value wet weight (L/kg)	Reference
Common carp	BCF	< 2	NITE 2002
Fish	BCF	< 20	NITE 2002

Since no experimental bioaccumulation factor (BAF) and few BCF data for DPG were available, a predictive approach was applied using available BAF and BCF models as shown in Table 5b below.

BCF and BAF estimates, corrected for potential biotransformation, were generated using the BCFBAF model (EPIsuite 2008). Metabolic rate constants were derived using an *in vivo* BCF normalization routine described further in Arnot et al. (2008a, 2008b and 2009). Since metabolic biotransformation rates are related to body weight and temperature (Hu and Layton 2001, Nichols et al. 2007), the BCFBAFWIN model provides a "normalized" metabolic rate constant ($k_{M,N}$) for a 10 g fish at 15°C. For DPG this screening level estimate is 10.1 /day. The middle-trophic-level fish was used to represent overall model output as suggested by the model developer and is generally representative of fish consumed by an avian or terrestrial piscivore based on its mass. After scaling the $k_{M,N}$ QSAR to a fish with a mass of 184 g (middle-trophic-level fish estimate) the rate constant is 4.9 (1/days). However, this estimate is uncertain since the k_M-QSAR model training and test sets have limited data for ionizing substances, particularly cationic substances.

Table 5b. Modelled data for bioaccumulation for DPG

Test organism	Model and model basis/reference	Endpoint	Value wet weight (L/kg)	Reference
Fish	BCFBAF Sub-model 1: linear regression	BCF	37.7	BCFBAF 2008
Fish	BCFBAF Sub-model 2: mass balance	BCF	22.34	BCFBAF 2008
Fish	BCFBAF Sub-model 3: Gobas-mass balance	BAF	22.34	BCFBAF 2008

The available evidence indicates that DPG is expected to have low bioaccumulation in fish. The metabolism-corrected BCF and BAF values are both 22.34 and the sub-model using linear-regression, which includes correction factors but does not explicitly consider k_M, predicts a BCF of 37.

The weight of evidence from the log D, log K_{ow}, measured BCF, and the modelled BCF and BAF data indicate that DPG has low bioaccumulation potential in fish. Therefore, based on the available empirical and kinetic-based modelled values, DPG does not meet the bioaccumulation criteria (BAF or BCF $\geq$ 5000) as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

Potential to Cause Ecological Harm

Ecological Effects Assessment

A - In the Aquatic Compartment

There is modelled and experimental evidence that DPG may cause acute harm to some species of aquatic organisms at moderate exposure concentrations (i.e., in the 1 – 100 mg/L range; see Tables 6a and 6b).

Table 6a. Empirical data for aquatic toxicity

Test organism	Type of test	Endpoint	Value (mg/L)	Reference
Algae *Selenastrum capricorntum*	Acute (96 hours)	EC_{50} [1]	1.7	Bayer 1990
Daphnia	Acute (48 hours)	EC_{50} [1]	17	Bayer 1990
Daphnia	Chronic (21 days)	NOEC [2]	0.6	Bayer 1990
		LOEC [3]	1.9	
		EC_{50} [1]	> 1.9 - < 6.0	
Medaka fish *Oryzias latipes*	Acute (48 hours)	LC_{50} [4]	10	Loeb and Kelly 1963
Bluegill Fish *Lepomis macrochirus*	Acute (96 hours)	LC_{50} [4]	9.6	Monsanto 1979a
Rainbow Trout *Oncorhynchus mykiss*	Acute (96 hours)	LC_{50} [4]	11	Monsanto 1979b
Fathead minnow *Pimephales promelas*	Acute (96 hours)	LC_{50} [4]	4.2	Monsanto 1979c

[1] EC_{50} – The concentration of a substance that is estimated to cause some effect on 50% of the test organisms.
[2] LC_{50} – The concentration of a substance that is estimated to be lethal to 50% of the test organisms.
[4] NOEC – The No-Observed-Effect Concentration is the highest concentration in a toxicity test not causing a statistically significant effect in comparison to the controls.
[5] LOEC – The Low-Observed-Effect Concentration is the lowest concentration in a toxicity test that caused a statistically significant effect in comparison to the controls.

The experimental data, shown in Table 6a, indicate that DPG has potential for moderate toxicity to aquatic organisms such as fish (medaka, bluegill, rainbow trout and fathead minnow) and invertebrates (*Daphnia*). There is evidence, that DPG might be more hazardous to some species of algae. The lowest acute value from reliable aquatic toxicity data is a 96 hour EC_{50} of 1.7 mg/L for algae (*Selenastrum capricorntum*).

Predicted ecotoxicity values obtained for DPG are shown in Table 6b.

Table 6b. Modelled data for aquatic toxicity

Test organism	Type of test	Endpoint	Value (mg/L)	Reference
Fish	Acute (96 hours)	LC_{50}[1]	10.75	ECOSAR 2008
			0.8	TOPKAT 2004
			32.6	OASIS Forecast 2005
Daphnia	Acute (96 hours)	EC_{50}[2]	1.30	ECOSAR 2008
			6.1	TOPKAT 2004
Green Algae	Acute (96 hours)	EC_{50}[2]	0.75	ECOSAR 2008

[1] LC_{50} – The concentration of a substance that is estimated to be lethal to 50% of the test organisms.
[2] EC_{50} – The concentration of a substance that is estimated to cause some effect on 50% of the test organisms.

A range of aquatic toxicity predictions were obtained from the various QSAR models considered. These results indicate that the substance is potentially hazardous to some species of aquatic organisms, including some species of algae (acute $LC/EC_{50} \leq 1.0$ mg/L).

The weight of evidence considering the available experimental and modelled data for DPG indicates that this substance is not expected to cause acute harm to aquatic organisms at low concentrations (nearly all acute EC_{50}s and LC_{50}s are > 1.0 mg/L). The lowest acute value from reliable aquatic toxicity data is a 96 hour EC_{50} of 1.7mg/L for algae (*selenastrum capricorntum*).

B - In Other Environmental Compartments

No suitable ecological effects studies were found for this compound in media other than water.

Ecological Exposure Assessment

No data concerning concentrations of this substance in water in Canada have been identified; therefore, environmental concentrations are estimated from available information, including estimated substance quantities, release rates, and the size of receiving water bodies.

A – Industrial Release

A site-specific exposure analysis was conducted for the aquatic compartment at a total of 3 sites where DPG was used as an additive in the production of rubber products. The quantity of the substance used at each site was in the range of 10 000–100 000 kg/year (Environment Canada 2010d). The maximum fraction lost from the production processes to wastewater prior to any wastewater treatment was conservatively estimated to be 0.5 % (OECD 2004). The wastewater containing DPG was then treated by off-site secondary

wastewater treatment systems The effluents from these treatment systems were then released to rivers or lakes and a dilution factor of 10 was used in deriving the predicted environmental concentrations (PECs) from the effluent concentrations. The estimated PECs for the 3 industrial sites ranged from 0.05 µg/L–15.4 µg/L (Environment Canada 2010d). These estimated PEC values represent the level of exposure in the receiving water near the point of the discharge from the wastewater treatment plant for each site.

Characterization of Ecological Risk

The approach taken in this ecological screening assessment was to examine relevant scientific and technical information and develop conclusions based on a weight-of-evidence approach and using precaution as required under CEPA 1999. Lines of evidence considered include results from a conservative risk quotient calculation, as well as information on persistence, bioaccumulation, toxicity, sources and fate of the substance.

DPG is expected to be persistent in water, soil and sediment; it is also expected to have a low bioaccumulation potential. The high importation volumes of DPG into Canada, along with information on its uses, indicate potential for widespread release into the Canadian environment. Once released into the environment, it will be found mainly in water when emissions are to water and there is no significant loss in water treatment plants. It has also been demonstrated to have moderate potential for toxicity to aquatic organisms.

A risk quotient analysis, integrating conservative estimates of exposure with toxicity information, was performed for the aquatic medium to determine whether there is potential for ecological harm in Canada. The site-specific industrial scenarios (considering the actual receiving water bodies) presented above yielded PECs ranging from 0.05 µg/L–15.4 µg/L (Environment Canada 2010d). A predicted no-effect concentration (PNEC) was derived from the acute toxicity value of 1.7 mg/L (the most sensitive valid experimental value) for algae by dividing this value by an assessment factor of 100 (to account for interspecies and intraspecies variability in sensitivity and extrapolation from an acute effect measured in the lab to a chronic no-effect value in the field) to give a value of 0.017 mg/L (17 µg/L). The resulting risk quotients (PECs/PNEC) were all less than 1, ranging from 0.003–0.885. Therefore, harm to aquatic organisms is considered unlikely at these sites. This information suggests that DPG is unlikely to be causing ecological harm in Canada.

Uncertainties in Evaluation of Ecological Risk

Uncertainties are present due to the lack of information on environmental concentrations in Canada of DPG. However this data gap was addressed by making conservative assumptions when estimating environmental concentrations that could result from industrial use of DPG.

There is uncertainty about the extent to which the positively charged substance with a relatively low log D_{ow} will partition to solids (sediment or soil).

The bioaccumulation assessment is limited by the fact that very few empirical bioaccumulation data were identified for DPG (although the measured BCF data indicate that DPG has very low bioaccumulation potential in aquatic organisms). This necessitated that predictions using models be generated. Although all predictions using models have some degree of error, the metabolism-corrected model outputs confirmed that DPG, given its structural characteristics, can be expected to have a low bioaccumulative potential.

Potential to Cause Harm to Human Health

Exposure Assessment

Environmental Media

No empirical data were identified in the published literature regarding directly measured concentrations of DPG in environmental media (air, water, soil and sediment) in Canada or elsewhere. In response to the section 71 survey, less than 100 kg of DPG was reported to be released to air, and similarly, less than 100 kg of the substance was reported to be released to water in Canada in 2006; no releases to land were reported (Environment Canada 2010b).

DPG was not detected in a 1978 Japanese survey of surface water and sediment (limits of detection in multiple analyses of water samples and sediment samples ranged from 2–50 ng/mL and 0.1–0.5 mg/kg, respectively) (Japan Ministry of Environment 2004).

Since DPG is used in the manufacturing of rubber for tires, it has been proposed (GDCh-BUA 1992; GDCh-BUA 2007) that a possible environmental source of exposure to DPG for the general population is airborne road dust containing tire debris. No studies have been identified that quantify DPG in atmospheric particulate matter in Canada or elsewhere. Tire debris contributes only a small percentage (1-10%) to the airborne traffic pollution (Pierson and Brachazek 1974; Fauser et al. 2002; GDCh-BUA 2007) and most material worn by tires becomes nonsuspendable particles deposited near the road (Pierson and Brachazek 1974). Additionally, the usual commercial loading of DPG in rubber manufacturing is 0.1–1.0 w/w % (GDCh-BUA 1992) and DPG is not expected to volatilize into the atmosphere given its low vapour pressure (3.97×10^{-6} mmHg) and low Henry's Law Constant (1.1×10^{-4} Pa·m^3/mole). It is expected that this substance, if present, is mostly encapsulated within the rubber matrix of tire wear particles, thereby limiting potential for exposure in the transportation corridor via the inhalation route. Based on the above considerations, exposure to DPG amongst the general population via airborne road dust containing tire debris is not expected to be significant.

The contribution of tire tread particles to soil near roadways (within 30 metres from roadway edge) has also been investigated. In California, the tread-rubber content ranged between approximately 0.02 to approximately 0.5 w/w % (equivalent to 5 mg/g of soil) in five soil samples collected close to a busy highway (Cadle and Williams 1979). Results from another study showed that the concentrations of tire debris were less than 1 mg per gram of soil near roads in Denmark (Fauser et al. 2002). Both studies showed that tire-tread concentrations in soil decreased with increasing distance from the roadway. Based on the maximum percentage of DPG loading in manufacture of tire rubber (1.0 w/w %) and the maximum potential tread-rubber content in soil (< 5 mg/g), the concentration of DPG in soil was assumed to be 0.05 mg/g and upper-bounding estimates of daily exposure to DPG from soil for various age groups of the general population were derived. These upper-bounding estimates, based on incidental ingestion of soil due to assumed proximity to roadways, range from 0.02 µg/kg-bw per day (20+ years of age) to 0.32 µg/kg-bw per day (0.5–4 years of age).[3] These estimates are considered to be conservative because they are based on conservative assumptions, i.e., maximum potential concentration of DPG in rubber and soil from within 30 m of a busy highway. Additionally, it is expected that accelerators are mostly consumed during the vulcanization process (GDCh-BUA 1992; ChemRisk 2008), a factor not accounted for in the exposure derivation.

Confidence in the exposure characterization for environmental media is considered to be low due to the lack of data available. Estimated exposures (based on tire debris content in soil) are considered to be upper-bounding as they are based on conservative assumptions. Confidence is high that exposure to DPG from environmental media and diet is not expected to be significant.

Consumer Products

According to the information available and industry data reported under section 71 of CEPA 1999, DPG is used in Canada to manufacture rubber material for tires and industrial applications (Environment Canada 2010b; May 2010 email from Risk Management Bureau, Health Canada to Existing Substances Division, Health Canada; unreferenced).

In a Japanese study, DPG was found in a packing coffee siphon (Baba 1980). This type of consumer product is considered to be uncommon in North America. Therefore, exposure to DPG from packing coffee siphon was not considered relevant. DPG is not used in food packaging in Canada.

[3] The following age groups were assumed to ingest the indicated amounts of soil incidentally each day: 0–6 months (assumed to weigh 7.5 kg), 30 mg of soil per day; 0.5–4 years (assumed to weigh 15.5 kg), 100 mg of soil per day; 5–11 years (assumed to weigh 31.0 kg), 65 mg of soil per day; 12–19 years (assumed to weigh 59.4 kg), 30 mg of soil per day, 20–59 years (assumed to weigh 70.9 kg), 30 mg of soil per day; 60+ years (assumed to weigh 72.0 kg), 30 mg of soil per day (Health Canada 1998).

Therefore, exposure to the general population to DPG from use of consumer products is not expected.

Health Effects Assessment

A summary of the available health effects information for DPG is presented in Appendix 1.

The European Commission has classified DPG as a Category 3 for reproductive toxicity ("substance causes concern for human fertility"), with the risk phrase R62 ("possible risk of impaired fertility") based on limited toxicity studies on DPG in experimental animals (European Commission 1998; ESIS 2009).

The reproductive and developmental toxicity of DPG has been evaluated in short-term and subchronic studies in mice, rats and hamsters. In a 15-week drinking water study (Bempong and Hall 1983), a time- and dose-dependent increase in the incidence of sperm abnormalities, and decreases in sperm counts and testes weights were reported in male C57BL/6J x DBA2 mice starting from the 6th week of exposure to DPG at 0, 4, or 8 mg/kg-bw per day. Histological examination of the testes of exposed mice revealed irregularly shaped seminiferous tubules and reduced numbers of spermatids and spermatozoa in the tubule lumens. When DPG-treated male mice in this study were mated with untreated females, a dose-dependent decrease in the fertility indices and implant numbers per pregnancy and an increase in foetal mortality were observed. However, in a 56-day gavage study, only a slight but statistically significant increase in sperm abnormalities was seen in male Swiss CD-1 mice treated with DPG at 16 mg/kg-bw per day; no effects on sperm parameters were observed at doses up to 4 mg/kg-bw per day. The implant numbers per pregnancy and foetal survival rate were comparable to controls when treated males were mated with untreated females in the follow-up reproductive study (Koëter et al. 1992). In 13-week oral diet toxicity studies (NTP 1995), significantly reduced sperm motility was observed at higher doses in DPG treated rats (at 1500 ppm, 121 mg/kg-bw per day) and in mice (at 3000 ppm, 573 mg/kg-bw per day). Depleted prostates, reduced absolute weights in prostates and testes, and decreased spermatogenesis were observed in rats at the highest dose level (3000 ppm, equivalent to 200 mg/kg- bw per day). The evaluation of female reproductive parameters revealed extended oestrus cycle lengths in rats (at 1500 ppm, 127 mg/kg-bw per day) and in mice (at 3000 ppm, 691 mg/kg-bw per day). A dose-dependent increase in sperm abnormalities was also observed in male golden Syrian hamsters treated *ad libitium* with DPG in the drinking water at 4 or 8 mg/kg-bw per day for 15 weeks (Bempong and Hall 1983).

In mice, Yasuda and Tanimura (1980) reported that a slight but statistically significant reduction in implant numbers in pregnant dams was observed after DPG treatment via gavage on gestation days (GD) 0 to 18 at 10 mg/kg-bw per day (the highest dose level tested). Retarded ossification in foetuses was only reported at the mid-dose (4 mg/kg-bw per day), but not at low (≤ 1 mg/kg-bw per day) or high (10 mg/kg-bw per day) doses. No overt signs of maternal toxicity were seen in dams.

In rats, slightly increased post-implantation losses, reduced foetal weights and increased incidence of foetuses with incomplete ossification or bent ribs were reported after dams were treated with DPG by gavage from GD 6 to 15 at 50 mg/kg-bw per day (the highest dose tested). Decreased maternal body weight gains and other clinical signs of toxicity were also reported in dams at this dose level (Monsanto 1986).

The only available carcinogenicity studies for DPG have study design and reporting limitations. Bempong (1986; cited in OECD 2002 as unpublished data) reported that lymph gland adenosarcomas were observed in mice in a 32-week oral toxicity study; however, this effect was limited to 3 of 50 animals in the low-dose (4 mg/kg-bw per day) group, and no tumours were observed in the high dose or control groups. In another insufficiently documented study, no pathological effects (neoplastic or non-neoplastic effects) were identified in mice after 21 months of oral exposure to DPG at up to 103 mg/kg-bw per day (Kurokawa and Ogawa; date not specified; cited in OECD 2002 as unpublished data). As only limited data were available with respect to the chronic toxicity of DPG, the outputs of predictive (Q)SAR models were also considered. Four different (Q)SAR models (DEREK, TOPKAT, CASETOX and Leadscope Model Applier) were used, which did not result in any alert for potential carcinogenicity associated with the molecular structure of DPG.

The potential genotoxicity of DPG has been assessed in *in vitro* and *in vivo* assays. The results are predominantly negative. In *in vivo* oral toxicity studies, DPG did not induce micronucleus formation in peripheral erythrocytes in male mice or chromosome aberrations in bone marrow cells in rats (Monsanto 1989; NTP 1995). DPG did not cause gene mutation in *Salmonella typhimurium, Escherichia coli* or *Saccharomyces cerevisiae* in most of the tests *in vitro* in the presence or the absence of metabolic activation[4]. Weakly positive responses for gene mutation in *Salmonella typhimurium* were reported by Bempong and Mantley (1985) in the presence and the absence of metabolic activation and also by Mortelmans et al. (1986) only in the presence of metabolic activation. *In vitro*, DPG tested negative for gene mutations in mouse lymphoma cells and Chinese hamster lung fibroblast V79 cells (Monsanto 1979d; Donner et al. 1983); it also did not induce chromosome aberrations in the lung and ovary cells of Chinese hamster (Monsanto 1992b; MHLW 2005).

Various short-term and subchronic oral toxicity studies were available for DPG. Significantly reduced mean body weight gains and decreased food intake (in diet studies only) were reported at dose levels of 50 mg/kg-bw per day and above in several short-term toxicity studies in rats (McCormick 1971; Monsanto 1980, 1985, 1986). In subchronic (90 day) diet studies, the lowest doses that caused similar health effects were 500 ppm (37 mg/kg-bw per day) in rats (Monsanto 1982a), and 750 ppm (133 mg/kg-bw per day) in mice (NTP 1995). Although altered organ weights or clinical chemistry/haematological parameters were frequently observed in these studies, they were considered by the investigators to be the results of reduced food intake or poor

[4] Reference list: Monsanto 1976; You et al. 1982; Crebelli et al. 1984b, 1985; Rannug et al. 1984; Mortelmans et al. 1986; Yamaguchi et al. 1991; NTP 1995; JETOC 1996; Enomoto et al. 2001.

health due to DPG exposure (NTP 1995; GDCh-BUA 1998; OECD 2002). Changes in lipid parameters caused by short-term oral exposure to DPG at 75 mg/kg-bw per day and above in rats were reported in some studies; however, no corresponding histopathological effects were recorded (Trendafilova and Picin 1971; Trendafilova 1971, 1972; Picin and Trendafilova 1972; Picin 1973). Reduced blood glucose levels (in both sexes) and increased platelet counts (in females only) were observed at 30 mg/kg-bw per day in rats in a 28-day study (Murata et al. 2001). High mortality rates were also found in high dose DPG treated rats in the studies described above (i.e. at doses above 100 mg/kg-bw per day) (Monsanto 1980, 1985; NTP 1995).

Oral exposure to DPG was associated with a reduction in thresholds of excitability of nerve and muscle, and decreased motor activity in rats and mice at dose levels greater than those inducing body weight changes (Orlov et al. 1973; Monsanto 1980, 1986; NTP 1995; MHLW 2005).

Limited information indicated that rats exposed to DPG dust at a concentration of 220 mg/m^3 via inhalation for 2 hours each day for 15 days could exhibit altered oxidation-reduction processes and alter nervous system function (Arkhangel'skaya and Roshchina 1963).

The only dermal study identified, although insufficiently documented, indicated that repeated dermal applications of DPG at 1000 mg/kg-bw per day did not induce systemic toxicity in rabbits (no further details were provided in the reference, McCormick 1971).

DPG is irritating to the eye and slightly irritating to the skin of rabbit (Kowalski and Bassendowska 1965; Monsanto Company 1977b, c). In humans, following workplace exposure to DPG, eye and mucous membrane irritations were reported (no further data were available, Arkhangel'skaya and Roshchina 1963). DPG showed no sensitizing effects in guinea pigs in a maximization test (MLPC 1995). When tested in human volunteers, 19 of the 49 test subjects displayed irritation reactions following the initial application of DPG in a patch test, and two were sensitized during the challenge phase (Monsanto 1982b). In contact dermatitis patients, positive skin reactions to DPG were occasionally reported (about 0.03–12% of the total tested subjects in approximately 4/5 of the studies) among a large number of patch tests[5].

In an occupational cohort study of workers of age 29 to 58 who had come into contact with DPG, in addition to other chemicals, over 3 to 15 years during production (no further information available), approximately 30% of the subjects reported various symptoms, including a high frequency of stomach/gall-bladder complaints, dermatitis and altered threshold of nerve-muscle irritability and a low frequency of liver metabolism

[5] References list: Meneghini et al. 1963; Agrup 1969; Rudzki and Kleniewska 1970; Baer et al. 1973; Reifferscheid 1979; Rajan and Khoo 1980; Lynde et al. 1982 ; Garcia-Perez et al. 1984; Suskind 1984; Liden 1989; Bajaj et al. 1988, 1991; Conde-Salazar et al. 1993; Saha et al. 1993; Bruze and Kestrap 1994; Kiec-Swierczynska 1995; Susitaival et al. 1995; Mancuso et al. 1996; Holness and Nethercott 1997; Nettis et al. 2002a, 2002b, 2003; Geier et al. 2003; Trattner et al. 2003; Comfere et al. 2005; Holden and Gawkrodger 2005; Katugampola et al. 2005; Piskin et al. 2006.

disorders (Orlov et al. 1973). However, due to the multiple chemical exposures and a lack of quantitative exposure levels, the study is insufficient for characterizing health effects of DPG.

There is no information available regarding the absorption of DPG from the respiratory tract. Orally administered DPG was readily absorbed from the gastrointestinal tract in rats, distributed rapidly, metabolized into three major and two minor unidentified metabolites, and excreted about equally in the urine and faeces (Ioannou and Matthews 1984). The absorption, distribution and excretion of DPG were not significantly affected by the route of administration in rats (e.g. oral or i.v. routes; Ioannou and Matthews 1984). No tissue accumulation was found in rabbits (Kazarinova et al. 1975) or mice (Hunter and Scully personal communication with Bempong; cited in Bempong and Hall 1983). The absorption of DPG through skin was low in rats with 10% absorption within 120 hours (approximately 0.08 %/hr). Following absorption, DPG distributed readily throughout the entire organism and was eliminated mainly via urine and faeces (Shah et al. 1985).

The confidence in the health effects database is considered to be moderate. However, there were no well-conducted chronic toxicity or carcinogenicity studies.

Characterization of Risk to Human Health

Based on consideration of the weight-of-evidence-based classification of DPG by the European Commission and the available health effects data, the critical effect associated with the oral exposure to DPG is reproductive toxicity. The lowest-observed-adverse-effect-level (LOAEL) for impaired fertility for DPG was identified as 4 mg/kg-bw per day in a subchronic oral toxicity study in mice. This was based on a dose-related increase in sperm abnormalities, decrease in sperm counts, decrease in testis weights and testicular histological changes in treated male mice, as well as a decrease in implant numbers and an increase in foetal deaths in untreated dams, after they were mated with DPG treated males.

Other health effects such as reduced body weight gains and decreased food intake were reported in experimental animals in short-term and subchronic oral toxicity studies conducted on DPG at dose levels greater than those inducing reproductive effects. A threshold approach is used to characterize the risk to human health.

Exposure of the general population to DPG in Canada may occur through incidental ingestion of soil containing tire debris deposited near roadways. Conservative estimates of this exposure range from 0.02 μg/kg-bw per day (20+ years of age) to 0.32 μg/kg-bw per day (0.5–4 years of age), based on a study of tire-rubber content in soil within 30 m of a highway and the maximum loading of DPG in rubber manufacturing. Comparison of the critical effect level of 4 mg/kg-bw per day (the LOAEL for impaired male fertility via oral route) to the upper-bounding estimate of exposure (0.32 μg/kg-bw per day) to DPG potentially present in tire particles in the soil results in a margin of exposure of 12,500.

This margin is considered adequate to address uncertainties in the health effects and exposure databases.

Uncertainties in Evaluation of Risk to Human Health

This screening assessment does not include a full analysis of the mode of induction of effects of DPG, nor does it take into account the possible differences in sensitivity between humans and experimental species. There are no well-conducted carcinogenicity studies available for DPG and the data regarding chronic exposure to DPG is also limited. In addition, only very limited information was available concerning the potential health effects of DPG following exposure via inhalation and dermal routes.

There is uncertainty in the characterization of exposure of the general population as no empirical data were identified regarding measured concentrations of DPG in environmental media (air, water, soil and sediment) in Canada or elsewhere. Estimated exposures are based on tire debris content in soil and considered to be upper-bounding as they are derived from conservative assumptions. There is uncertainty related to secondary uses of tires (recycling, energy production), and to accidental fires at disposal sites where tires are stored; however there is insufficient data to characterize potential bystander exposure from this source. Confidence is high that exposure to DPG from environmental media and diet is not expected to be significant, especially considering that accelerators are mostly or completely consumed during the vulcanization process in rubber manufacturing (GDCh-BUA 1992; ChemRisk 2008).

Lack of information regarding DPG content in rubber formulations for Canadian consumer products is also a source of uncertainty. However, available information did not identify a presence of DPG in Canadian consumer products.

Although DPG is irritating to the eyes, respiratory system and skin, it cannot be concluded that it is a sensitizer, due to the negative results obtained in animal studies and to the limitations of the studies conducted in humans (i.e. the possibility of cross sensitization). Although there is uncertainty in assessing its sensitization potential, exposure from consumer products via the dermal route is not expected based on the industrial use pattern of DPG.

Conclusion

Based on the information presented in this final screening assessment, it is concluded that DPG does not meet the criteria in paragraphs 64*(a)* and *(b)*, as it is not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity or that constitute or may constitute a danger to the environment on which life depends. Additionally, DPG meets the criteria for persistence, but does not meet the criteria for

bioaccumulation potential, as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

Based on the available information on its potential to cause harm to human health, it is concluded that DPG does not meet the criteria in paragraph 64*(c)* of CEPA 1999, as it is not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

It is therefore concluded that DPG does not meet any of the criteria under section 64 of CEPA 1999.

This substance will be considered for inclusion in the Domestic Substances List inventory update initiative. In addition and where relevant, research and monitoring will support verification of assumptions used during the screening assessment.

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Appendix 1: Summary of health effects information for DPG

Endpoint	LD_{50}/LC_{50} or lowest/no effect levels[1]/results
Laboratory animals and *in vitro*	
Acute toxicity	**Lowest oral LD_{50}** (mouse) = 150 (female)-211 (male) mg/kg-bw (Hasegawa 1989) **Other oral LD_{50}** (rabbit) = 246 mg/kg-bw (Vlasyuk 1978). **Other oral LD_{50}** (guinea pig) = 250 mg/kg-bw (Marhold 1986). **Other oral LD_{50}** (rat) = 350 mg/kg-bw (Monsanto Company 1977a). **Dermal LD_0** (rabbit) > 2000 mg/kg-bw (Monsanto Company 1992a). **Inhalation LC_0** (species not specified) = 500 mg/m^3 (Valade et al. 1949).
Short-term repeated-dose toxicity	**Oral LOAELs:** **Lowest oral LOAEL** = 50 mg/kg-bw per day (1000 ppm) based on reduced body weight gain and decreased food intake in rats (strain, sex and group sizes not specified) exposed to 100 or 1000 ppm (equivalent to 5 or 50 mg/kg-bw per day) DPG in the diet for 28 days (McCormick 1971). **Other oral LOAEL** = 56 mg/kg-bw per day (500 ppm) based on significant dose-related reduction in body weight gain and decreased food consumption at 500 ppm and above in both sexes of Sprague-Dawley rats (5 per sex per group) exposed to 0, 300, 500, 800, 1500 or 3000 ppm DPG (0, 36, 56, 73, 119 or 200 mg/kg-bw per day) in the diet for 14 days. Other clinical signs of toxicity were observed in higher dose groups including emaciation from 800 ppm, reduced body tone and piloerection from 1500 ppm, ataxia, hunched posture, subdued appearance and hair loss at 3000 ppm. Statistically significant reductions ($p<0.001$) in the absolute weights of the heart, liver, kidneys and spleen were observed in male rats from 800 ppm and above and in females at 3000 ppm (for brain, heart and spleen only) . A statistically significant increase in relative brain weight was reported in males in all dose groups and in females in 500 and 1500 ppm dose groups. The author claimed that the differences observed in absolute and relative organ weight profiles between control and treated rats are attributed to the reduction in body weight gain in DPG treated rats. Two males and three females died at 3000 ppm. Gross pathological examination did not reveal any gross lesions in DPG treated rats (Monsanto 1980). **Other oral LOAEL** = 64 mg/kg-bw per day (750 ppm) based on reduced final mean body weights/body weight gains and decreased food intake at 750 ppm and above in both sexes of F344/N rats (5 per sex per group) exposed to 0, 250, 500, 750, 1500 or 3000 ppm DPG in diet (equivalent to 0, 22, 45, 64, 121 or 200 mg/kg-bw per day for males; 0, 23, 44, 65, 127 or 166 mg/kg- bw per day for females) for 14 days. Clinical signs of toxicity, including ruffled fur and thin appearance were reported in both sexes of rats at 3000 ppm. No treatment-related gross lesions were observed (NTP 1995).

Endpoint	LD_{50}/LC_{50} or lowest/no effect levels[1]/results
	LOELs: **Lowest oral LOEL**= 30 mg/kg-bw per day based on decreased blood glucose level, brown coloured liver and increased salivation in both sexes of Crj: CD (SD) IGS rats (5 per sex per group) exposed to 0, 10, 30 or 90 mg/kg-bw per day by gavage for 28 days (with 14 days of recovery period for control and high dose groups). Increased platelet counts were observed only in female rats at 30 mg/kg-bw per day. Increased urea nitrogen and total billirubin levels, and elevated alanine aminotransferase and alkaline phosphatase activities in blood were observed in high dose males. Prone and lateral position, staggering gait, decreased locomotor activity and startle reflex, increased frequency of hydrophobic changes in the renal tubules, significantly diminished food consumption and reduced body weight gain were observed in both sexes of animals at high dose level. One male and three female rats in high dose groups died during treatment. No effects on weights or on gross or microscopic appearance of the reproductive organs were reported in both sexes of rats (Murata et al. 2001). **Inhalation study:** LOAEC ~220 mg/m^3 based on marked disturbance in the intensity of oxidation-reduction processes, functionally disturbed nervous system and transient increase in blood pressure in rats (strain, sex and group sizes not specified) exposed to DPG dust 2 hours per day for 15 days by inhalation (Arkhangel'skaya and Roshchina 1963). **Dermal study:** Rabbits (strain, sex and group sizes not specified) were exposed to both dry and paste forms of DPG on their skin at 1000 mg/kg-bw for 10 repeated applications; no signs of systemic toxicity were observed (McCormick 1971). Other studies: Verchovski 1952; Burov 1964; Trendafilova and Picin 1971; Trendafilova 1971, 1972; Picin and Trendafilova 1972; Picin 1973; NTP 1995.
Subchronic toxicity	**Lowest oral LOAEL** = 37 mg/kg-bw per day (500 ppm) based on significant reduced mean body weight and decreased food consumption in both sexes of Sprague-Dawley rats (15 per sex per group) exposed to 0, 50, 150 or 500 ppm DPG in the diet (equivalent to 0, 4, 11 or 37 mg/kg-bw per day) for 90 days. A statistically significant decrease in the absolute weights and an increase in the relative weights of various organs (heart, liver, kidney and spleen weights in males and brain weights in females) were also observed in high groups. The slight changes in clinical chemistry (increase in alanine aminotransferase and alkaline phosphatase) and in haematology (increase in white blood cell count) were not considered by investigators to have been of toxicological significance. No macroscopic intergroup differences of any significance were observed at necropsy. Histopathological examination showed no specific lesion that could be attributed to dosing with DPG. **Oral LOAEL for reproductive toxicity** =37 mg/kg-bw per day (500 ppm) based on increased relative uterus weights in females and relative testes weights in males. No histopathological changes or

Endpoint	LD_{50}/LC_{50} or lowest/no effect levels[1]/results
	weight changes in other reproductive organs were reported (Monsanto 1982a). **Other oral LOAEL** = 64 mg/kg-bw per day (750 ppm) based on reduced body weight and decreased food intake at this dose level and marked at higher dose levels in both sexes of F344/N rats (10 per group) exposed to 0, 250, 500, 750, 1500 or 3000 ppm DPG in the diet (equivalent to 0, 22, 45, 64, 121 or 200 mg/kg-bw per day for males; 0, 23, 44, 65, 127 or 166 mg/kg- bw per day for females) for 13-weeks. Overt signs of toxicity including ruffled fur, thin appearance, discolouration of body parts, salivation, hypoactivity, convulsions and seizures; hunched posture, ptosis, ataxia and dyspnea were observed in both sexes of rats at 1500 ppm and above. Abnormalities of clinical chemistry (increased alkaline phosphatase activity and bile acid concentration; decreased total protein, creatinine, cholesterol, and triglyceride concentrations) and abnormalities of haematology (increased erythrocyte counts, hematocrit values, and hemoglobin concentrations) were also observed at 1500 ppm and above. Histopathological exams revealed depletion and necrosis in tissues from a number of organs in the highest dose treated males and females. Significantly decreased organ weights were also observed in two high doses treated rats. All the effects observed at two high doses were considered by the study author as the result of lower food intake, reduced body weight gain and poor body condition. All females and 3 males in the top dose groups died before the end of the study (NTP 1995). **Oral LOAEL for reproductive toxicity** = 64 mg/kg-bw per day (750 ppm) based on uterine hypoplasia at 750 ppm and above and extended oestrus cycle length at 1 500 ppm were observed in females. Significantly decreased sperm motility at 1 500 ppm, depletion of the prostate, hypospermia, decreased spermatogenesis and reduced absolute weights of the prostate gland and testis at 3 000 ppm were reported in males (NTP 1995). **Other oral LOAEL** = 133 mg/kg-bw per day (750 ppm) based on decreased body weight and body weight gain (in the absence of any marked reduction in food intake) in both sexes of $B6C3F_1$ mice (10 per sex per group) exposed to 0, 250, 500, 750, 1500 or 3000 ppm in the diet (equivalent to 0, 48, 92, 133, 266 or 573 mg/kg-bw per day in males; 0, 53, 112, 150, 303 or 691 mg/kg-bw per day in females) for 13-weeks. Hair loss, abnormal posture and ptosis were observed at 1 500 ppm and above. Significant decreased absolute organ weights and increased relative organ weights observed at 1 500 ppm and above were evaluated as not a specifically toxic response but rather were correlated with the clearly reduced body weights by the study author. **Oral LOAEL for reproductive toxicity** = 573(male) - 691(female) mg/kg-bw per day (3000 ppm) based on reduced sperm density/motility in males and extended oestrus cycle length in females (NTP 1995). Other studies: Arkhangel'skaya and Roshchina 1963; Orlov et al. 1973. **No dermal or inhalation subchronic toxicity studies were identified.**
Chronic toxicity/ carcinogenicity	In an insufficiently documented study, both sexes of $C57BL/J6xDBA_2$ hybrid mice (50 per sex per group) were exposed to DPG in the diet at 0, 4 or 8 mg/kg-bw per day for 32 weeks followed by a 10-16 week observation period. No

Endpoint	LD_{50}/LC_{50} or lowest/no effect levels[1]/results
	tumours were observed at the end of the treatment; however, 3 of the 50 low dose treated mice developed lymphatic adenocarcinomas after the observation period. No such tumours were reported in the high dose or the control groups. Transient enlargement of spleens were also reported (no further details available) (Bempong 1986). In an insufficiently documented study, both sexes of ddy mice (30 or 60 per sex in treatment or control groups respectively) were exposed to DPG at 0, 20, 60, 180 or 540 ppm (equivalent to 0, 3, 10, 35, 103 mg/kg-bw per day) in the diet for 21 months. No pathological effects (neoplastic or non-neoplastic) attributable to treatment were noted in any dose group (no further details available) (Kurokawa and Ogawa; cited in OECD 2002). **No dermal or inhalation chronic toxicity studies were identified.**
Genotoxicity and related endpoints: *in vivo*	**Micronucleus formation** **Negative in males/ equivocal in females**: Peripheral erythrocytes of B6C3F1 mice orally dosed at 0, 250, 500, 750, 1500 or 3000 ppm of DPG for 13-weeks (equivalent to 0, 38, 75, 114, 231 or 457 mg/kg-bw per day in males and 0, 46, 93, 141, 285 or 577 mg/kg-bw per day in females) (NTP 1995). **Negative**: Mice (no further details) (Bempong, unpublished data cited in Monsanto 1987). **Chromosome aberration** **Negative**: Bone marrow cells of Sprague-Dawley rats after single oral dose of 300 mg/kg-bw per day of DPG (Monsanto 1989).

Endpoint	LD_{50}/LC_{50} or lowest/no effect levels[1]/results
Genotoxicity and related endpoints: *in vitro*	**Chromosome aberration** **Negative**: Chinese hamster lung CHL/IU cells with and without metabolic activation (MHLW 2005). **Negative**: Chinese hamster ovary (CHO) cells with and without metabolic activation (Monsanto, 1992b). **Gene mutation** **Negative**: Chinese hamster V79 cells without metabolic activation in HGPRT test (Donner et al. 1983). **Negative**: Mouse lymphoma L5178Y cells (TK+/- assay) with and without metabolic activation (Monsanto 1979d). **Negative***: Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 with or without metabolic activation (Monsanto 1976; You et al. 1982; Rannug et al. 1984; Crebelli et al. 1984, 1985; Yamaguchi et al. 1991; NTP 1995; Enomoto et al. 2001). **Positive (weakly)**: *Salmonella typhimurium* strains TA98, 100 with metabolic activation (Mortelmans et al. 1986); strains TA98, 100, 1535, 1537, 1538 with and without metabolic activation (Bempong and Mantley 1985). **Negative**: *Escherichia coli* WP2uvra with and without metabolic activation (JETOC 1996). **Negative**: *Saccharomyces cerevisiae* D4 with and without metabolic activation (Monsanto 1976). **Inhibition of the colony formation** Inhibited 50% of colony formation in Human HeLa-S3 cells without metabolic activation (Baba 1980). **Host mediated mutagenic assay** Ten C57BL mice (sex not specified) per each dosage level were given single i.p. injections of DPG at a final concentration of 0.036, 0.36, 3.6 or 36.0 mg/kg-bw per day. After incubating of *Salmonella typhimurium* strain TA100 with peritoneal, urine or faecal material collected from mice, a time- and dose-related mutation was reported in bacteria incubated with faeces from treated mice. No mutation was induced by peritoneal fluid or urine (Bempong and Mantly 1985).

Endpoint	LD_{50}/LC_{50} or lowest/no effect levels[1]/results
Reproductive toxicity	**Lowest oral LOAEL** = 4 mg/kg-bw per day based on a significant nonlinear increase in the frequency of sperm abnormalities (from week 6), decreased sperm counts (from week 7) and testis weights (from week 5) and irregularly shaped seminiferous tubules in male C57BL/6J x DBA2 mice (20 per group) exposed to 0, 4 or 8 mg/kg-bw/day of DPG in acidified drinking water for up to 105 days. At scheduled scarification on 1, 3, 5, 7, 9 and 15 weeks, histological examination of the testes of exposed mice revealed irregularly shaped seminiferous tubules with no defined basement membrane, a loss of interstitial cells, and reduced numbers of spermatids and spermatozoa in the tubule lumens in a time-dependent manner. After 7 day of exposure, the males were mated at weekly intervals to untreated females. A dose-dependent decrease in fertility indices / numbers of implants per pregnancy and increase in early and late foetal deaths (from week 7) were reported in untreated pregnant females (sacrificed on day 13 of pregnancy). **Lowest oral LOAEL** = 4 mg/kg-bw per day based on a dose-dependent increase in incidence of sperm abnormalities (started from day 30 and evidenced from day 75) in male golden Syrian hamsters (5 per group) exposed to 0, 4 or 8 mg/kg-bw per day of DPG in the drinking water for up to 80 days. No other adverse effects were reported (Bempong and Hall 1983). **Other oral LOAEL** = 16 mg/kg-bw per day based on a slight, but statistically significant increase in sperms with folded tails but normal heads in male CD-1 mice (25 per group) exposed to 0, 0.06, 0.25, 1, 4 or 16 mg/kg-bw per day of DPG by gavage for 56 days. No other treatment related effects were found in the highest dose treated mice in the microscopic examination of the testes or on the frequency of total sperm abnormalities. No treatment related body/organ weight changes, microscopic observation or death were reported in treated males. After high doses treated males (4 and 16 mg/kg-bw per day) mated with unexposed females at the end of the treatment, no adverse effects on fertility or reproductive performance were observed in both sexes of adult mice, and no changes on embryo development or other litter parameters were reported (dams were sacrificed on day 14 of pregnancy). No maternal body weight effects were seen in untreated dams (Koëter et al. 1992).
Developmental toxicity	**Lowest oral LOAEL** = 10 mg/kg-bw per day based on significant reduced mean number of implants in pregnant ICR-JCL mice (20 per group) exposed to 0, 0.25, 1, 4, or 10 mg/kg-bw per day of DPG by gavage on gestation days 0 to 18. No maternal toxicity was observed and there were no significant differences between treated and control groups in the percentage of dead foetuses, average litter size, sex ratio, or mean body weights. The incidence of external or skeletal abnormalities in treated groups was similar to that of the control group. A retarded ossification of the talus was seen in the foetuses of the dams treated with 4.mg/kg-bw per day of DPG, but not at low or high doses (Yasuda and Tanimura 1980). **Other oral LOAEL** = 50 mg/kg-bw per day based on significantly reduced foetal weight and an increase in the incidence of foetuses with incomplete ossification or bent ribs in the offspring of pregnant Sprague-Dawley rats (group of 25) exposed to 0, 5, 25 or 50 mg/kg-bw per day by gavage from

Endpoint	LD_{50}/LC_{50} or lowest/no effect levels[1]/results
	gestation day 6 to 15(sacrificed at gestation day 20). No other treatment-related foetal malformations were reported. The foetal sex ratios, the mean numbers of viable foetuses, implantation sites and corpora lutea were comparable to the vehicle control group. An increase in the post-implantation losses was observed in the high dose dams. **LOAEL for maternal toxicity** = 50 mg/kg-bw per day based on a statistically significant reduction in mean body weight/body weight gain and clinical signs of toxicity (hair loss, lethargy, tachypnea, decreased limb tone, prostrate and ataxia, etc.) in pregnant rats. No effect on maternal survival was reported at any dose levels (Monsanto 1986). In a range-finding teratology study, pregnant Sprague-Dawley rats (5 per group) were exposed to 0, 10, 50, 100, 150 or 200 mg/kg-bw per day of DPG by gavage (in 0.5% aqueous Methocel) from gestation days 6 to 15. All the rats in the top two dose groups and four in the 100 mg/kg-bw per day dose group died between gestation days 7 to 11. No effect on post-implantation losses, number of yellow bodies, number of implantations or foetal viability was observed in survivors. **LOAEL for maternal toxicity** = 50 mg/kg- bw per day based on a marked decrease in body weight gain was observed at this dose level and above. Lethargic behaviour and ataxia occurred in four rats in the 50 mg/kg/day dose group and one rat in the 100 mg/kg/day dose group (primarily during gestation days 6 to 9). Prostrate behaviour and tachypnea were observed in one rat in each of the 50 and 100 mg/kg/day dose groups. Clinical observation noted similar neuro-behavioural and locomotive abnormalities with the premature decedents that were similar to those of the survivors. The necropsy examinations of decedents showed congestion of various organs (Monsanto 1985).
Sensitization	In a maximization test, 10 guinea pigs (sex and strain not specified) were challenged epicutaneously by 0.5ml of 25% of DPG following the day 1 intracutaneous induction (0.1 ml of 1% of DPG) and day 8 epicutaneous induction (0.5ml of 25% of DPG). There were no cutaneous reactions attributable to the sensitization potential of DPG reported in the treated guinea pigs (MLPC 1995).
Irritation	**Skin irritation** No skin irritation was reported in a Draize test when 0.5 g of ground sample moistened with water was applied to the skin of rabbits (strain, sex and group size not specified) for 24 hours (Monsanto Company 1977c). Slight irritation caused by DPG was reported in another Draize test in rabbits without study details (Kowalski and Bassendowska 1965). **Eye irritation** In eye irritation tests, 6 rabbits (sex and strain not specified) were exposed to DPG in the eyes for 24 hours (no test detail provided). Slight irritation occurred at 20 mg of DPG and marked irritation at a dose level of 100 mg (Kowalski and Bassendowska 1965; Monsanto 1977b).

Endpoint	LD_{50}/LC_{50} or lowest/no effect levels[1]/results
Humans	
Sensitization	In a patch test in human volunteers, 49 of human subjects were tested with 70 % of DPG in petrolatum, no significant positive reactions were observed after the first induction application. 19 of the 49 subjects displayed irritation during the subsequent induction exposures. Two subjects displayed positive reactions during the 2-week challenge phase (Monsanto 1982b). A number of reports of patch tests involving DPG (in footwear allergens, rubber chemicals/additives or 0.5 to 2% of DPG in petrolatum/ or Plastibase) have been conducted on large groups of contact dermatitis patients world wide. Positive skin reactions were reported at a ratio of 0.03 to 12% of the total tested subjects in most of the studies. Positive reactions were found without correlation with the types or dose levels of DPG tested (Meneghini et al. 1963; Agrup 1969; Rudzki and Kleniewska 1970; Baer et al. 1973; Reifferscheid 1979; Rajan and Khoo 1980; Lynde et al. 1982 ; Garcia-Perez et al. 1984; Suskind 1984; Liden 1989; Bajaj et al. 1988, 1991; Conde-Salazar et al. 1993; Saha et al. 1993; Bruze and Kestrap 1994; Kiec-Swierczynska 1995; Susitaival et al. 1995; Mancuso et al. 1996; Holness and Nethercott 1997; Nettis et al. 2002a, 2002b, 2003; Geier et al. 2003; Trattner et al. 2003; Comfere et al. 2005; Holden and Gawkrodger 2005; Katugampola et al. 2005; Piskin et al. 2006).
Epidemiological Studies	**In an occupational cohort study** on workers of age 29 to 58 (no detail provided, without control group; presumably conducted in Russia) who had come into contact with DPG for over 3-15 years. High frequency of adverse effects including gastritis, cholangitis, cholecystitis, neurological disturbances and dermatitis; and low frequency of adverse effects including bronchial asthma, rhinitis, neuropathy, polyarthritis, hypertonia, lithiasis, disturbed liver function, changes in protein metabolism and increased bilirubin concentration were seen in about 30% of the workers (Orlov et al. 1973). **In an occupational cohort study** on workers who had been accidentally exposed to DPG previously (no detail provided, without control group; presumably conducted in Russia), adverse effects such as eyelid pain, eye redness, bitter taste, painful oesophagus, flabby gums, reduced/absence of acidity of gastric juice and tending to achylia were observed (Arkhangel'skaya and Roshchina 1963).

[1] LD_{50}/LC_{50} = median lethal dose/median lethal concentration; LOEL/LOEC = lowest-observed-effect level/concentration; LOAEL/LOAEC = lowest-observed-adverse-effect level/concentration; NOAEL/NOAEC = no-observed-adverse-effect level/concentration.