# Screening Assessment for the Challenge

## Benzo[*b*]thiophen-3(2*H*)-one, 6-chloro-2-(6-chloro-4-methyl-3-oxobenzo[*b*]thien-2(3*H*)-ylidene)-4-methyl- (Pigment Red 181)

## Chemical Abstracts Service Registry Number 2379-74-0

**Environment Canada**
**Health Canada**

**September 2010**

## 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 on Benzo[b]thiophen-3(2H)-one, 6-chloro-2-(6-chloro-4-methyl-3-oxobenzo[b]thien-2(3H)-ylidene)-4-methyl-, Chemical Abstracts Service Registry Number 2379-74-0. This substance, also known as Pigment Red 181, was identified as a high priority for screening assessment and included in the Challenge because it had been found to meet the ecological categorization criteria for persistence, bioaccumulation potential and inherent toxicity to non-human organisms and is believed to be in commerce in Canada.

The substance, Pigment Red 181, was not considered to be a high priority for assessment of potential risks to human health, based upon application of the simple exposure and hazard tools developed by Health Canada for categorization of substances on the Domestic Substances List. Therefore, this assessment focuses principally on information relevant to the evaluation of ecological risks.

Pigment Red 181 is a special-purpose pigment for polystyrene and similar polymers. It is also used in personal care products. The substance does not naturally occur in the environment. It is not reported to be manufactured in Canada; however, between 100 and 1000 kg of the pigment were imported into the country in 2006, both as an industrial chemical and in imported coloured products.

Based on reported use patterns in Canada and on certain assumptions, most of the substance is exported from Canada in finished products, and the portion that remains in Canada is believed to be released ultimately to wastewater either during the manufacture of coloured items or after consumer use of such items. There are no releases predicted to air and soil. Pigment Red 181 presents very low experimental solubility in water and low solubility in octanol. It is present in the environment primarily as micro-particulate matter that is not volatile and is relatively chemically stable, and it has a tendency to partition by gravity to sediments if released to surface waters, and to soils if released to air.

Based on its physical and chemical properties, Pigment Red 181 is expected to be persistent in water, soil and sediment. New experimental data relating to its solubility in n-octanol and water suggest that this pigment has a low potential to accumulate in the lipid tissues of organisms. The substance meets the persistence criteria but does not meet the bioaccumulation criteria as set out in the *Persistence and Bioaccumulation Regulations*. In addition, new toxicity predictions that take into account revised estimates of bioaccumulation potential suggest that saturated solutions of the substance do not cause acute harm to aquatic organisms but could potentially cause chronic harm to sensitive organisms.

For this screening assessment, two conservative exposure scenarios were used. In one scenario an industrial operation (user of the pigment) discharges Pigment Red 181 into the aquatic environment. In the second scenario, use of Pigment Red 181 in cosmetics by

consumers results in the release of the substance to the aquatic environment. In both scenarios, predicted environmental concentrations in water were below the predicted no-effect concentration for sensitive aquatic organisms, except at one site. The exception is likely an overestimate given the number of conservative assumptions used. Therefore, releases of Pigment Red 181 are not expected to cause harm to aquatic organisms

Based on available information, and a survey under section 71 of CEPA 1999, exposure of the general population to Pigment Red 181 from environmental media (ambient and indoor air, drinking water, soil and sediment) is expected to be negligible. The general population of Canada may be exposed to Pigment Red 181 from use of cosmetics, including some personal care products, as it is an ingredient in some products on the Canadian market.

Pigment Red 181 was not identified as posing a high hazard to human health. Based on consideration of the hazard profile of Pigment Red 181 and upper-bounding estimates of exposure to cosmetics, including some personal care products containing this substance, and toxicokinetics of the substance, a concern for human health was not identified.

Based on the information available, it is concluded that Pigment Red 181 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 the information available, it is concluded that Pigment Red 181 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. Pigment Red 181 meets the persistence criteria but does not meet the bioaccumulation criteria as set out in the *Persistence and Bioaccumulation Regulations*.

Based on the information available, it is concluded that Pigment Red 181 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 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 2006a), that 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 Benzo[*b*]thiophen-3(2*H*)-one, 6-chloro-2-(6-chloro-4-methyl-3-oxobenzo[*b*]thien-2(3*H*)-ylidene)-4-methyl- was identified as a high priority for the assessment of ecological risk as it had been found to be persistent, bioaccumulative and inherently toxic to aquatic organisms and is believed to be in commerce in Canada. The Challenge for this substance was published in the *Canada Gazette* on March 14, 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 physical and chemical properties, bioaccumulation potential, hazard and uses of the substance were received.

Although Benzo[*b*]thiophen-3(2*H*)-one, 6-chloro-2-(6-chloro-4-methyl-3-oxobenzo[*b*]thien-2(3*H*)-ylidene)-4-methyl- was determined to be a high priority for assessment with respect to the environment, it did not meet the criteria for GPE or IPE and high hazard to human health based on classifications by other national or international agencies for carcinogenicity, genotoxicity, developmental toxicity or reproductive toxicity. Therefore, this assessment focuses principally on information relevant to the evaluation of ecological risks.

Screening assessments focus on information critical to determining whether a substance meets the criteria as set out in section 64 of CEPA 1999[1]. Screening assessments examine scientific information and develop conclusions by incorporating a weight-of-evidence approach and precaution.

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, stakeholder research reports and from recent literature searches, up to September 2009 ecological section and December 2009 for the human health section of the document. Key studies were critically evaluated; modelling results may have been used to reach conclusions.

When available and relevant, information presented in hazard assessments from other jurisdictions was considered. The final screening assessment does not represent an exhaustive or critical review of all available data. Rather, it presents the most critical studies and lines of evidence pertinent to the conclusion.

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 portion of this assessment has undergone external written peer review/consultation. Additionally, the draft of this screening assessment was subject to a 60-day public comment period. While external comments were taken into consideration, the final content and outcome of the screening assessment remain the responsibility of Health Canada and Environment Canada. Approaches used in the screening assessments under the Challenge have been reviewed by an independent Challenge Advisory Panel.

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

[1] 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 us

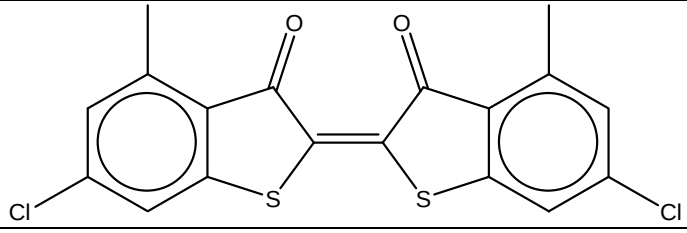
## Substance Identity

### Substance Name

For the purposes of this document, Benzo[*b*]thiophen-3(2*H*)-one, 6-chloro-2-(6-chloro-4-methyl-3-oxobenzo[*b*]thien-2(3*H*)-ylidene)-4-methyl- will be referred to as Pigment Red 181, one of the common names of this substance.

**Table 1. Substance identity for Pigment Red 181**

| | |
|---|---|
| **Chemical Abstracts Service Registry Number (CAS RN)** | **2379-74-0** |
| **DSL name** | **Benzo[*b*]thiophen-3(2*H*)-one, 6-chloro-2-(6-chloro-4-methyl-3-oxobenzo[*b*]thien-2(3*H*)-ylidene)-4-methyl-** |
| **National Chemical Inventories (NCI) names[1]** | *Benzo[b]thiophen-3(2H)-one, 6-chloro-2-(6-chloro-4-methyl-3-oxobenzo[b]thien-2(3H)-ylidene)-4-methyl-* (TSCA, AICS, PICCS, ASIA-PAC, NZIoC)<br>*6-chloro-2-(6-chloro-4-methyl-3-oxobenzo[b]thien-2(3H)-ylidene)-4-methylbenzo[b]thiophene-3(2H)-one* (EINECS)<br>*Vat Red 1* (ENCS, PICCS)<br>*C.I. vat red 001* (ECL)<br>*C.I. PIGMENT RED 181* (PICCS)<br>*Benzo[b]thiophen-3(2H)-one,6-chloro-2-(6-chloro-4-methyl-3-oxobenzo[b]thien-2(3H)-ylidene)-4-methyl-* (PICCS)<br>*D & C RED 30* (PICCS)<br>*C.I. VAT RED 1* (PICCS) |
| **Other names** | *11484 Red; 5,5'-Dichloro-3,3'-dimethyl-thioindigo; 6,6'-Dichloro-4,4'-dimethylthioindigo; Ahcovat Pink FFD; Ahcovat Printing Pink FF; Amanthrene Pink FF; Amanthrene Pink FFD; Amanthrene Pink FFWP; C.I. 73360; Calcoloid Pink FFC; Calcoloid Pink FFD; Calcoloid Pink FFRP; Calcoloid Printing Pink FFE; Calcophyl Red FF; Calophyl Pink ZFF; Chemithrene Brilliant Pink R; Ciba Brilliant Pink FR; Ciba Brilliant Pink R; Ciba Pink FF; D and C Red No. 30; D&C Red No. 30; Daltolite Pink FF; Durindone Pink FF; Durindone Pink FF-FA; Durindone Printing Pink FF; Fast Pink Y; Fenanthren Brilliant Pink R; Fenanthren Pink R Spura; Fenidon Pink R; Helanthrene Brilliant Pink R; Helanthrene Pink R; Helindon Pink CN; Helindon Pink R; Helindone Pink CN; Hostavat Brilliant Pink R; Indanthren Brilliant Pink R; Indanthren Brilliant Pink RB; Indanthren Brilliant Pink RP; Indanthren Brilliant Pink RS; Indanthren Brilliant Rose R; Indanthrene Brilliant Pink R; Indanthrene Pink R; Japan Red 226; Lithosol Fast Pink SVP; Mikethrene Brilliant Pink R; Nihonthrene Brilliant Pink R; Nyanthrene Brilliant Pink R; Oracet Pink RF; Oralith Brilliant* |

| | |
|---|---|
| | *Pink R; Palanthrene Brilliant Pink R; Paradone Brilliant Pink R; Permanent Pink; Pink FFT; Red No. 226; Romantrene Brilliant Pink FR; Sandothrene Brilliant Pink R; Sanyo Threne Brillant Pink IR; Solanthrene Brilliant Pink F-R; Solanthrene Brilliant Pink R; Solanthrene Brilliant Pink RF; Sulfanthrene Pink FFD; Thioindigo Brilliant Pink Zh; Thioindigo Brilliant Pink ZhP; Thioindigo, 6,6'-dichloro-4,4'-dimethyl-; Tina Brilliant Pink R; Tyrian Brilliant Pink I-R; Vat Pink FF; Vat Pink R; Vat Printing Pink FF; [D2,2'(3H,3'H)-Bibenzo[b]thiophene]-3,3'-dione, 6,6'-dichloro-4,4'-dimethyl-; 6-Chloro-2-(6-chloro-4-methyl-3-oxobenzo[b]thien-2(3H)-ylidene)-4-methylbenzo[b]thiophen-3(2H)-one* |
| **Chemical group (DSL Stream)** | Discrete organics |
| **Major chemical class or use** | Polycyclic pigments |
| **Major chemical sub-class** | Thioindigo pigments |
| **Chemical formula** | $C_{18}H_{10}Cl_2O_2S_2$ |
| **Chemical structure** |  |
| **SMILES**[2] | O=C(c(c(S1)cc(c2)Cl)c2C)C1=C(Sc(c3c(cc4Cl)C)c4)C3=O |
| **Molecular mass** | 393.31 g/mol |

[1] National Chemical Inventories (NCI). 2007: 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); ELINCS (European List of Notified Chemical Substances); ENCS (Japanese Existing and New Chemical Substances); NZIoC (New Zealand Inventory of Chemicals); PICCS (Philippine Inventory of Chemicals and Chemical Substances); and TSCA (Toxic Substances Control Act Chemical Substance Inventory).

[2] Simplified Molecular Input Line Entry System

## Physical and Chemical Properties

The pigment industry synthesizes organic pigments that it considers to have low to very low solubility (i.e., < 1 mg/L and < 0.01 mg/L, respectively) in nearly all solvents (Herbst and Hunger 2004; Lincke 2003). This arises from its desire to produce colorants that will retain their colour for a long time and in various types of substrates.

The majority of organic pigments generally do not exist as individual molecules but are principally particles in the submicron range. The pigment powder is typically composed of particles (i.e., the crystal lattice of a pigment), aggregates and agglomerates. Manufacturers usually provide the physical specifications of their pigments, which include the average particle size of the pigment powder. In doing so, users can determine which pigment is the most appropriate to colour their product(s) since performance is chiefly controlled by the particle size distribution (Herbst and Hunger 2004).

Pigments have high molecular weights (i.e., generally > 300 g/mol), are solid particles at room temperature, decompose at temperatures greater than 220°C and have extremely low solubility in water (Danish EPA 1999). In addition, these substances generally have limited solubility in *n*-octanol, have a negligible vapour pressure and are stable under environmental conditions, as would be expected from their intended use as pigments.

Few experimental data are available for Pigment Red 181. At the Environment Canada-sponsored Quantitative Structure-Activity Relationship (QSAR) Workshop in 1999 (Environment Canada 2000), Environment Canada and other invited modelling experts identified many structural classes of pigment and dyes as "difficult to model" using QSARs. The physical and chemical properties of many of the structural classes of dyes and pigments (including acid and disperse dyes) are not amenable to model prediction because they are considered "out of the model domain of applicability" (e.g., structural and/or property parameter domains). Therefore, to determine potential utility, the domains of applicability of QSAR models to dyes and pigments are evaluated on a case-by-case basis.

Table 2 shows some experimental and modeled physical and chemical properties of Pigment Red 181 that are relevant to its environmental fate. Because of a lack of experimental data for Pigment Red 181 and similar pigments, QSAR models have been used to estimate a number of endpoints despite the uncertainties inherent in using this approach. These models are mainly based on fragment addition methods, i.e., they rely on the structure of a chemical. Key studies from which experimental data were reported for some of these properties were critically reviewed for reliability. These reviews (Robust Study Summary) are found in Appendix I.

**Table 2. Physical and chemical properties for Pigment Red 181**

| Property | Type | Value[1] | Temperature (°C) | Reference |
|---|---|---|---|---|
| Melting point[2] (ºC) | Modelled | 220.68 | | MPBPWIN 2008 |
| Boiling point (ºC) | Modelled | 517.3 | | MPBPWIN 2008 |
| | | 529.1 | | ACD 2009 |
| Density ($kg/m^3$) | Modelled | 1583 | 20 | ACD 2009 |
| Vapour pressure (Pa) | Experimental | $4.0 \times 10^{-12}$ ($3.4 \times 10^{-14}$ mm Hg) [1] | 25 | Baughman and Perenich 1988 |
| | Modelled | $1.08 \times 10^{-8}$* ($8.1 \times 10^{-11}$ mm Hg) [1] | 25 | MPBPWIN 2008 |
| | | $3.7 \times 10^{-9}$ | 25 | ACD 2009 |
| Henry's Law constant ($Pa \cdot m^3/mol$) | Modelled | $3.09 \times 10^{-8}$* ($3.05 \times 10^{-13}$ $atm \cdot m^3/mol$) [1] | | HENRYWIN 2008 |
| Log $K_{ow}$ (Octanol-water partition coefficient) (dimensionless) | Modelled | 5.92 | | KOWWIN 2008 |
| | | 4.277 | 25 | ACD 2009 |
| Log $K_{oc}$ (Organic carbon-water partition coefficient) (dimensionless) | Modelled | 4.17 | | PCKOCWIN 2008 |
| | | 3.7 | 25 | ACD 2009 |
| Log $C_o/C_w$ (n-octanol solubility/water solubility) | Experimental | 2.06* | 22–23 | Study Submission 2009 |

| Property | Type | Value[1] | Temperature (°C) | Reference |
|---|---|---|---|---|
| Water solubility (mg/L) | Experimental | 0.0046* | 22–23 | Study Submission 2009 |
| | Modelled | 0.0299 | 25 | WSKOWWIN 2008 |
| | | 0.39 | 25 | ACD 2009 |
| Octanol solubility (mg/L) | Experimental | 0.53 | 22–23 | Study Submission 2009 |
| $pK_a$ (Acid dissociation constant) (dimensionless) | Modelled | Non-ionizing | | ACD 2005 |
| Minimum-maximum cross-sectional diameter ($D_{Max}$) in (nm) | Modelled | 1.73 – 1.75 | | CPOPs 2008 |

Abbreviations: $K_{oc}$, organic carbon-water partition coefficient; $K_{ow}$, octanol-water partition coefficient.
[1] Values in parentheses represent the original ones as reported by the authors or as estimated by the models.
[2] The term "melting point" is used but this could be better referred to as a decomposition point since pigments are known to char at high temperatures (greater than 200°C) rather than melt.
*Value used for fate modelling.

## Sources

Pigment Red 181 does not naturally occur in the environment.

Recent information was collected through industry surveys conducted for the years 2005 and 2006 under *Canada Gazette* notices issued pursuant to section 71 of CEPA 1999 (Canada 2006b, 2009). In 2006, no company reported manufacturing Pigment Red 181 above the 100 kg/year reporting threshold. Fewer than four companies reported importing a combined total of between 100 and 1000 kg of Pigment Red 181. In 2005, no companies reported manufacturing Pigment Red 181 above the 100 kg/year threshold. Fewer than four companies reported importing between 100 and 1000 kg each of the substance in 2005. In both 2005 and 2006, the substance was reported to be imported in coloured products and in bulk as an industrial chemical. In addition, 10 Canadian companies and one American industry association identified themselves as having a stakeholder interest in the substance in 2006 (Environment Canada 2006, 2008a).

According to information submitted under the section 71 survey, a large proportion of the substance imported into Canada is incorporated into products and subsequently exported.

The quantity reported to be manufactured, imported or in commerce in Canada during the calendar year 1986 (during the development of the DSL) was 0 kg. However, the substance met DSL eligibility criteria during 1984–1985.

Elsewhere, Pigment Red 181 is used in the United States. According to the information collected by the U.S. EPA, in the years 1986, 1990, 1998, and 2002, import/usage quantities were in the range of 4.5–226 tonnes per year (US EPA 1986–2002). Pigment Red 181 is listed in the European Inventory of Existing Commercial Chemical Substances (EINECS) but has not been reported as either a high production volume (HPV) or a low production volume (LPV) chemical (ESIS 2008). In addition, according to the Substances in Preparations in Nordic Countries database (SPIN 2008), this chemical was used in Sweden and Denmark in the years 2000 to 2007. From 2000 to 2002, 1.1 tonnes of Pigment Red 181 were used per year in Denmark. However, other information on exact use quantities and use patterns is not available to the public.

## Uses

Pigment Red 181 is a special-purpose pigment for polystyrene and similar polymers, and is used in cosmetics (Herbst and Hunger 2004).

Information provided in the section 71 surveys indicated that business activities associated with the use of Pigment Red 181 in Canada in 2005 and 2006 were: Health and Personal Care Stores; Warehousing and Storage; and Toiletries, Cosmetics and Sundries Wholesaler-Distributors (Environment Canada 2006, 2008a). One company reported importing Pigment Red 181 within a nail polish product in 2006 (Environment Canada 2008a).

The following uses, pertaining to the years 1984 – 1986, were identified for Pigment Red 181 during the compilation of the Domestic Substances List (DSL):

Colorant - Pigment/Stain/Dye/Ink,
Pigment, Dye and Printing Ink,
Textile, Primary Manufacture.

Under Health Canada's Cosmetic Notification System (CNS), approximately 2000 products were notified to contain Pigment Red 181. Products notified include makeup for body, face, and eyes; deodorant; lipstick; manicure preparation; skin moisturizer and cleanser; massage oil; fragrance; bath preparations; shampoo; and dentifrice (CNS 2009). These products were notified to CNS under various common names including: C.I. VAT Red 1, C.I. 73360, C.I. 73360 as a component with other ingredients, Red 30 Lake, Red 30 Lake and methicone, RED 30 LAKE notified as a component with other ingredients, Castor Seed Oil/Red 30 Lake, and Red 30. Pigment Red 181 (under the

names D&C Red 30 and D&C Red 30 Lake) is also listed as an ingredient in pharmaceutical products (MediResources Inc. 2009).

Pigment Red 181 is listed in the *Food and Drug Regulations* in section C.01.040.2(3)(a) as a colouring agent permitted in drugs for internal and external use under the name Helindone Pink CN (D&C Red No. 30; C.I. No. 73360)(Canada 1978). Thus, this colouring agent is permitted in pharmaceutical drugs, natural health products and veterinary drugs in Canada (2009 personal communication from Natural Health Products Directorate, Health Canada to Existing Substances Risk Assessment Bureau, Health Canada; unreferenced). Although listed in the Natural Health Products Ingredient Database (NHPID) as permitted in natural health products, it is not listed in the Licensed Natural Health Products Database (LNHPD) and thus is not present in current licensed natural health products (LNHPD 2009; NHPID 2010).

In Canada, food additives permitted for use as food colours are listed in Table III of Division 16 of the *Food and Drug Regulations* (Canada [1978]). Pigment Red 181 is not listed in Table III, nor is it approved for any other food additive use in Canada. It is also not approved for use as a colour additive in foods in the United States (US FDA 2009) or as a food colour in the European Commission (1994). Additionally Pigment Red 181 is not expected to be used in food packaging materials or formulations of incidental additives (2010, personal communication from Food Directorate, Health Canada; unreferenced).

## Releases to the Environment

Releases of Pigment Red 181 are not reported as part of Environment Canada's National Pollutant Release Inventory. The companies importing Pigment Red 181 as an industrial chemical reported releases of small amounts of the substance to water (Environment Canada 2009a). No other information concerning release of Pigment Red 181 to the environment in Canada has been identified. The total importation of Pigment Red 181 into Canada (both as an industrial chemical and in coloured products) in 2006 was reported in the range of 100–1000 kg (Environment Canada 2008a). Therefore, releases of this substance to the Canadian environment are expected to be low.

A method has been developed by Environment Canada to estimate a substance's losses during different stages of its life cycle, including its fate within a finished product or article (Environment Canada 2008b). This method consists of a life cycle analysis and a spreadsheet tool (Mass Flow Tool or MFT) that integrates information on the manufacturing, importation and use data available for the substance. Starting with an identified mass of the substance, each life cycle stage is subsequently evaluated until all of the mass is accounted for. Relevant factors are considered, uncertainties recognized and assumptions may be made during each stage, depending on information available. The estimated losses represent the complete mass balance of the substance over the life cycle of the substance and include releases to wastewater and other receiving compartments (land, air), chemical transformation, transfer to recycling activities and

transfer to waste disposal sites (landfill, incineration). However, unless specific information on the rate or potential for release of the substance from landfills and incinerators is available, the method does not quantitatively account for releases to the environment from disposal. Ultimately, the estimated losses provide a first tier in the exposure analysis of a substance and help to estimate environmental releases and focus exposure characterization later in the assessment.

In general, releases of a substance to the environment depend upon various losses from its manufacture, industrial use, and/or consumer/commercial use. These losses can be grouped into seven types: (1) discharge to wastewater; (2) emission to air; (3) loss to land; (4) chemical transformation; (5) disposal to landfill; (6) loss to incineration; and (7) disposal through recycling (i.e., recycling is deemed a loss and not considered further). They are estimated using regulatory survey data, industry data and data published by different organizations. The discharge to wastewater refers to raw wastewater prior to any treatment by either public or private wastewater systems. In a similar manner, the loss via chemical transformation refers to changes in a substance's identity that may occur within the manufacture, industrial use, and consumer/commercial use stages, but excludes those during waste management operations such as incineration and wastewater treatment. The loss to land includes unintentional transfer or leakage to soil or pave/unpaved surfaces during the substance's use and service life (e.g., from the use of agricultural machinery or automobiles). The loss to land, however, does not include transfers subsequent to a substance's use and service life (e.g., land application of biosolids and atmospheric deposition).

The losses estimated for Pigment Red 181 over its lifecycle (based on conservative assumptions) are presented in Table 3 (Environment Canada 2009b). Pigment Red 181 is not manufactured in Canada above reporting thresholds, so estimated losses are based on import quantities reported in 2006.

**Table 3. Estimated Losses of Pigment Red 181 during Its Lifecycle**

| Type of Loss | Proportion (%) | Pertinent Lifecycle Stages |
|---|---|---|
| Wastewater | 36.2 | Formulation into an article, and consumer/commercial use |
| Air emission | 0 | |
| Land | 0 | |
| Chemical transformation | 0 | |
| Landfill | 0 | |
| Incineration | 0 | |
| Recycling | 0 | |
| Export (in coloured products) | 63.8[1] | |

[1] Based on information received in response to *Canada Gazette* notice issued pursuant to section 71

Pigment Red 181 is estimated to be released to wastewater at 36.2% as a consequence of industrial and consumer usage. As worst-case estimates for losses from industrial usage, it is assumed that Pigment Red 181 imported in bulk (as an industrial chemical) is

incorporated into products and repackaged in containers designed for consumer uses. Conservatively, a loss of 5 % of the industrial chemical can occur from that type of operation, a loss of 3 % can occur from the cleaning of chemical containers and 2 % from the cleaning of process equipment (US EPA 2007). All of these releases would be to industrial wastewater. It is important to keep in mind that repackaging operations may or may not occur in Canada. For loss from consumer usage, it is anticipated that 95% of the substance used in consumer products is lost down the drain to wastewater.

The above loss estimates indicate that Pigment Red 181 has a potential for release to the environment. In general, wastewater routed though wastewater treatment facilities is a common source for releases of substances to surface water and wastewater sludge or biosolids is a source of substances to soil following land application.

Although there is the possibility that other consumer/commercial products containing Pigment Red 181 may be imported into Canada in addition to those reported as a result of industry surveys conducted pursuant to Section 71 of CEPA 1999, no information is available on the quantity of such imports. It is anticipated that the life cycle stages and proportional losses resulting from use of these other products would not be significantly different from those considered and estimated above. However, the actual mass of the substance lost from each of the life cycle stages may be somewhat higher than the estimates provided above, if such information was available for consideration.

Pigment Red 181 is used in cosmetics such as lipstick, skin cleanser and nail polish (Environment Canada 2006, 2008a; CNS 2009). It is conservatively assumed that the total mass of Pigment Red 181 contained in products of this type that are used in Canada will have down-the-drain release to wastewater systems across the country.

The losses estimated above are based on the assumption that Pigment Red 181 is likely to be released to the environment from both point (industrial) sources and disperse (consumer) sources.

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## Environmental Fate

Pigment Red 181 has a very low vapour pressure and a low estimated Henry's Law constant of ~ $10^{-8}$ Pa·$m^3$/mol. This pigment is not expected to volatilize at environmentally realistic temperatures, and will thus not be subject to long-range atmospheric transport.

The particulate character of Pigment Red 181 should have a key influence on its fate in the environment. Its relatively large particle size and high density (density = 1583 kg/$m^3$), together with its chemical stability (non-ionizing) and low aqueous solubility (water solubility = 0.0046 mg/L), indicate that it will partition by gravity to sediments if released to surface waters, and will tend to remain in soils if released to air.

# Persistence and Bioaccumulation Potential

## Environmental Persistence

Because of its very low solubility in water, this pigment may be considered not available for aerobic biodegradation. It is expected that the characteristics imparted to pigments would result in these substances being persistent in the environment. The Color Pigments Manufacturers Association, Inc. (CPMA 2003) has indicated that pigments are designed to be durable or persistent in the environment in order to provide colour to finished coatings, inks and paints.

No experimental degradation data for Pigment Red 181 have been identified. Given the ecological importance of the water compartment, the fact that most of the available biodegradation models apply to water, and the fact that Pigment Red 181 is expected to be released to this compartment, persistence in water was primarily examined using predictive QSAR models for biodegradation. Pigment Red 181 does not contain functional groups expected to undergo hydrolysis.

Table 4 summarizes the results of available QSAR models for degradation in water and air.

**Table 4. Modelled data for degradation of Pigment Red 181**

| Fate process | Model and model basis | Model result and prediction | Extrapolated half-life (days) |
|---|---|---|---|
| AIR | | | |
| Atmospheric oxidation | AOPWIN 2000[1] | $t_{1/2}$ = 2.3 hours | < 2 |
| Ozone reaction | AOPWIN 2000[1] | $t_{1/2}$ = 6.5 days | > 2 |
| Primary biodegradation | | | |
| Biodegradation (aerobic) | BIOWIN 2000[1] Sub-model 4: Expert Survey (qualitative results) | 2.8[2] "biodegrades fast - weeks" | < 182 |
| Ultimate biodegradation | | | |
| Biodegradation (aerobic) | BIOWIN 2000[1] Sub-model 3: Expert Survey (qualitative results) | 1.7[2] "biodegrades slowly" | ≥ 182 |
| Biodegradation (aerobic) | BIOWIN 2000[1] Sub-model 5: MITI linear probability | -0.09[3] "biodegrades very slowly" | ≥ 182 |
| Biodegradation (aerobic) | BIOWIN 2000[1] Sub-model 6: MITI non-linear probability | 0.0015[3] "biodegrades very slowly" | ≥ 182 |
| Biodegradation (aerobic) | CATABOL c2004–2008 % BOD | 0.073 "biodegrades very slowly" | ≥182 |

[1] EPI Suite (2008)
[2] Output is a numerical score from 0 to 5.
[3] Output is a probability score.

In air, a predicted atmospheric gas-phase oxidation half-life value of 2.3 hours (see Table 4) demonstrates that this substance is likely to be rapidly oxidized. The substance is predicted to react more slowly with ozone, with a half-life value of 6.5 days. Therefore, it is expected that reactions with hydroxyl radicals will be the most important gas-phase fate process in the atmosphere for Pigment Red 181. Although it is recognized that the substance does not partition significantly to air, with a half-life of 2.3 hours via reactions with hydroxyl radicals, Pigment Red 181 is considered to be not persistent in air.

Although there is model evidence (BIOWIN 4) for relatively fast primary biodegradation, the identities of the primary degradation products are not known. Model results related to complete mineralization (ultimate biodegradation) of the substance indicate that Pigment Red 181 does not biodegrade fast, with a predicted half-life value in water of >182 days.

Using an extrapolation ratio of 1:1:4 for a water: soil: sediment biodegradation half-life (Boethling et al. 1995) and an ultimate biodegradation half-life value in water of > 182 days, the half-life in soil is also > 182 days and the half-life in sediments is > 365 days. This indicates that Pigment Red 181 is also expected to be persistent in soil and sediment.

Based on all of the above, Pigment Red 181 meets the persistence criteria in water, soil and sediment (half-lives in soil and water ≥ 182 days and half-life in sediment ≥ 365 days), but 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**

No experimental bioaccumulation factor (BAF) and/or bioconcentration factor (BCF) data for Pigment Red 181 were available. The log $K_{ow}$ value of 5.92 for Pigment Red 181 modelled by KOWWIN suggests that this chemical has high potential to bioaccumulate in biota (see Table 2).

The partitioning of a substance into n-octanol is considered a good indicator of a substance's potential to partition into the lipid phase of aquatic biota (Bertelsen et al. 1998). For pigments, it has been observed that a reduced solubility in n-octanol translates into a similarly reduced BCF and BAF in aquatic organisms (Banerjee and Baughman 1991). Instead of the modelled log $K_{ow}$ value, the ratio of an experimental solubility of a substance in octanol ($C_o$) and water ($C_w$), or the log $C_o/C_w$ (see Table 2), can be used to estimate log $K_{ow}$ (Cole and Mackay 2000), and BCFs and BAFs may be estimated by substituting log $C_o/C_w$ for log $K_{ow}$ in QSAR-based bioaccumulation models. This approach was used for Pigment Red 181 because newly identified empirical data suggest that model-estimated log $K_{ow}$ values (e.g., 5.9; KOWWIN 2000) are too high in view of the substance's low solubility in n-octanol. Pigment Red 181 has a measured solubility of 0.53 mg/L in n-octanol and 0.0046 mg/L in water. The log $C_o/C_w$ is therefore 2.06. BCF and BAF estimates using this value are presented in Table 5.

**Table 5. Fish BAF and BCF predictions for Pigment Red 181**

| Test organism | Endpoint | Log $C_o/C_w$ used in model | Value (L/kg wet weight) | Reference |
|---|---|---|---|---|
| Fish | BAF | 2.06 | 8.5 | Arnot and Gobas 2003 (Gobas BAF Middle Trophic Level) |
| Fish | BCF | 2.06 | 8.5 | |
| | | 2.06 | 2.76 | BCFWIN 2000 |
| Fish | BCF | 2.06 | 8.3 | Baseline BCF model (Dimitrov et al. 2005) |

The modified Gobas BAF middle trophic level model for fish predicts a BAF of 8.5 L/kg, indicating that Pigment Red 181 does not have the potential to bioaccumulate and biomagnify in the aquatic environment. This estimate considers metabolic transformation utilizing the metabolic biotransformation rate estimate ($k_M$) of 0.53/day. With a biotransformation rate ($k_M$) of 0/day (no biotransformation), the modified Gobas BAF middle trophic level model for fish predicts a BAF of 8.9 L/kg and a BCF of 8.7 L/kg. This indicates that biotransformation has little effect on the bioaccumulation potential of Pigment Red 181. The middle trophic level fish was used to represent overall model output as suggested by the model developer and is most representative of fish weight likely to be consumed by an avian or terrestrial piscivore. The results of BCF model calculations provide additional evidence supporting the low bioconcentration potential of this substance.

There is limited bioaccumulation data available for Pigment Red 181. Therefore, available data on molecular weight and cross-sectional diameter have also been considered in order to determine the bioaccumulation potential of this substance.

Recent investigations relating fish BCF data and molecular size parameters (Dimitrov et al. 2002, 2005) suggest that the probability of a molecule crossing cell membranes as a result of passive diffusion declines significantly with increasing maximum diameter ($D_{max}$). The probability of passive diffusion decreases appreciably when the maximum diameter is greater than ~1.5 nm and much more so for molecules having a maximum diameter of greater than 1.7 nm. Sakuratani et al. (2008) have also investigated the effect of cross-sectional diameter on passive diffusion in a BCF test set of about 1200 new and existing chemicals. They observed that substances that do not have a very high bioconcentration potential (BCF < 5000) often have a $D_{max}$ of > 2.0 nm and an effective diameter ($D_{eff}$) > 1.1 nm.

However, as Arnot et al. (2010) have noted there are uncertainties associated with the thresholds proposed by Dimitrov et al. (2002, 2005) and Sakuratani et al. (2008) since the BCF studies used to derive them were not critically evaluated. Arnot et al. (2010) pointed out that molecular size influences solubility and diffusivity in water and organic phases (membranes), and larger molecules may have slower uptake rates. However, these same kinetic constraints apply to diffusive routes of chemical elimination (i.e., slow in =

slow out). Thus, significant bioaccumulation potential may remain for substances that are subject to slow absorption processes, if they are slowly biotransformed or slowly eliminated by other processes. Consequently, when evaluating bioaccumulation potential molecular size information should be considered with care, and used together with other relevant lines of evidence in a weight of evidence approach

Pigment Red 181 has a molecular weight of 393.31 g/mol and a Dmax = 1.73 – 1.75 nm, indicating a potential for a significantly reduced uptake rate from water and reduced in vivo bioavailability of the substance. In addition, the high modelled thermal decomposition and boiling point data (220 and 517-530 degrees C, respectively) for Pigment Red 181 indicate that the substance is relatively chemically stable and also is indicative of low potential bioavailability. For example, Chu and Yalkowsky (2009) found that in general, high melting compounds are less likely to be well absorbed than lower melting compounds for any given dose. Also, Kim et al (2007) stated that high melting point and limited solubility in either water or oil-based solvents often results in poor *in vivo* availability.

Combined with the experimental result that Pigment Red 181 has low solubility in water and octanol (Table 2) the available evidence indicates that Pigment Red 181 is expected to have a low bioaccumulation potential due to its physical and chemical properties which result in a very low uptake rate either from the gills or gut of biota. Any portion of the substance transmitted across membranes is likely then transformed by in vivo metabolism or eliminated via growth dilution.

Based on all of the above, Pigment Red 181 is estimated to have a low bioaccumulation potential. Considering the available evidence, Pigment Red 181 does not meet the bioaccumulation criteria (BCF, BAF ≥ 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

Since no experimental aquatic toxicity data or suitable analog substances are available for Pigment Red 181, models were used to estimate the potential for aquatic toxicity. Aquatic toxicity data for Pigment Red 181 was estimated with ECOSAR (2000) by using the calculated log ($C_o/C_w$) value of 2.06 as correction factor. A similar model correction using experimental data could not be performed using the TOPKAT and AIEPS models as their results are based on the estimated log $K_{ow}$ and so are likely to significantly overestimate toxicity.

Table 6 contains predicted ecotoxicity values that were used in the QSAR weight-of-evidence approach for aquatic toxicity (Environment Canada 2007).

**Table 6. Modelled data for aquatic toxicity**

| Test organism | Type of test | Endpoint | Value (mg/L) | Reference |
|---|---|---|---|---|
| Fish | Acute (96 hours) | $LC_{50}$[1] | 270* | ECOSAR 2000 |
| Fish | Chronic | Chronic value | 26* | ECOSAR 2000 |
| *Pimephales promelas* (Fathead Minnow) | Acute (96 hours) | $LC_{50}$[1] | 0.0786* | TOPKAT 2004 |
| *Pimephales promelas* (Fathead Minnow) | Acute (96 hours) | $LC_{50}$[1] | 0.57* | AIEPS 2003–2007 |
| *Daphnia* | Acute (48 hours) | $LC_{50}$[1] | 157* | ECOSAR 2000 |
| *Daphnia* | Chronic | Chronic value | 15* | ECOSAR 2000 |
| *Daphnia magna* | Acute (48 hours) | $LC_{50}$[1] | 1.0* | TOPKAT 2004 |
| *Daphnia magna* | Acute (48 hours) | $LC_{50}$[1] | 20.4* | AIEPS 2003–2007 |
| Green algae | Acute (96 hours) | $EC_{50}$[2] | 69* | ECOSAR 2000 |
| Green algae | Chronic | Chronic value | 25* | ECOSAR 2000 |
| *Pseudokirchneriella subcapitata* | Acute (72 hours) | $EC_{50}$[2] | 0.7* | AIEPS 2003–2007 |

[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 toxic sublethal effect on 50% of the test organisms.
*Value >water solubility of 0.0046 mg/L.

A range of aquatic toxicity predictions were obtained from the various QSAR models considered. The ECOSAR results all indicate low acute toxicity to organisms ($LC/EC_{50}$ >10 mg/L) while the TOPKAT and AIEPS results, expected to overestimate toxicity as noted above, indicate that the Pigment Red 181 could be highly hazardous to aquatic organisms (i.e. acute $LC/EC_{50}$ < 1.0 mg/L). All the predicted toxicity values are nevertheless well above the substance's measured water solubility of 0.0046 mg/L.

These results suggest that Pigment Red 181 is unlikely to cause acute effects at saturation, but given the magnitude of the lowest predicted acute toxicity value for fish ($LC_{50}$ = 0.0786 mg/L), there may be potential for chronic toxicity to sensitive fish species at concentrations below the measured water solubility value of 0.0046 mg/L.

### B - In Other Environmental Compartments

No 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 size of receiving water bodies.

### A – Industrial Release

The aquatic exposure of Pigment Red 181 is expected if the substance is released from an industrial use to a wastewater treatment plant and the treatment plant discharges its effluent to a receiving water body. The concentration of the substance in the receiving water near the discharge point of the wastewater treatment plant is used as the predicted environmental concentration (PEC) in evaluating the aquatic risk of the substance. It can be calculated using the equation

$$C_{water-ind} = \frac{1000 \times Q \times L \times (1-R)}{N \times F \times D}$$

where

| | |
|---|---|
| $C_{water-ind}$: | aquatic concentration resulting from industrial releases, mg/L |
| Q: | total substance quantity used annually at an industrial site, kg/yr |
| L: | loss to wastewater, fraction |
| R: | wastewater treatment plant removal rate, fraction |
| N: | number of annual release days, d/yr |
| F: | wastewater treatment plant effluent flow, $m^3/d$ |
| D: | receiving water dilution factor, dimensionless |

As Pigment Red 181 is used industrially and is expected to be released to water, a conservative industrial release scenario is used to estimate the aquatic concentration of the substance with the help of Environment Canada's (2009c) Industrial Generic Exposure Tool – Aquatic (IGETA). The scenario is made conservative by assuming that the total quantity of the substance used by Canadian industry is used by one single industrial facility and the loss to sewer is high at 5% of the total quantity resulting from the cleaning of chemical containers and process equipment. The scenario also assumes that the release occurs 250 days per year, typical for small and medium-sized facilities. It is assumed to be sent to a local sewage treatment plant (STP) with a 21.6% removal rate for the substance - estimated by the Simple Treat 3.0 model (SimpleTreat 1997) - and a low end ($10^{th}$ percentile) effluent flow rate of 3.9 $m^3$ per second. The concentration of Pigment Red 181 in the STP effluent is assumed to be diluted by a factor of 10 in the receiving water. Based on the above assumptions, the substance at a total quantity of 1000 kg/yr for industrial use yields a PEC of 0.000047 mg/L (Environment Canada 2009d).

**B – Consumer Release**

As Pigment Red 181 is found in consumer products and can be released to water, Mega Flush, Environment Canada's spreadsheet tool was employed to estimate the substance concentration in multiple water bodies receiving sewage treatment plant effluents to which consumer products containing the substance may have been released (Environment Canada 2009e). The spreadsheet tool provides these estimates for approximately 1000 release sites across Canada based on some conservative assumptions.

The assumptions made include:

- loss to sewer at 100%,
- sewage treatment plant removal rate estimated at 0.0 % in case of no treatment,
- number of annual release days at 365 days/year,
- receiving water dilution factor in the range of 1 to 10.

The PEC of Pigment Red 181 in the receiving water bodies was estimated to be in the range of 0 to 0.0015 mg/L. The estimate is based on a total of 1000 kg/year for the quantity of the substance used by consumers (based on the upper limit of the amount of Pigment Red 181 imported into Canada in 2006). The equation and inputs used to calculate the PEC are described in Environment Canada (2009f).

**Characterization of Ecological Risk**

The approach taken in this ecological screening assessment was to examine various supporting 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.

Pigment Red 181 is expected to be persistent in water, soil and sediment, but it is also expected to have a low bioaccumulation potential. The substance is expected to be released into the environment, based on its uses. Once released into the environment, it will be found mainly in water and sediments. In addition, new toxicity predictions that take into account revised estimates of log Co/Cw suggest that saturated solutions of the substance do not cause acute harm to aquatic organisms but could potentially cause chronic harm to sensitive 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.

A conservative predicted no-effect concentration (PNEC) was derived from the lowest estimated toxicity value identified—an acute value of 0.0786 mg/L for fathead minnow, *Pimephales promelas*. This value was selected as the critical toxicity value, and divided by an assessment factor of 100 to account for uncertainties in extrapolating from acute to

chronic effects and from a laboratory value to a predicted no-effect value in the field. This yielded a precautionary PNEC of 0.000786 mg/L. This value is considered a precautionary PNEC as no acute effects were observed at saturation (water solubility = 0.0046 mg/L) and some potential chronic toxicity is assumed.

When compared to the conservative PEC calculated above for industrial releases to water (0.000047 mg/L), the resulting risk quotient (PEC/PNEC) is 0.06.

For exposure resulting from down-the-drain releases using a very conservative consumer use scenario, Mega Flush results estimate that the predicted no-effects concentration (PNEC) would be exceeded at only one site (i.e., risk quotients > 1 at 0.1% of all sites), with a maximum risk quotient of 1.9.

When Pigment Red 181 is released into a water body, it is likely deposited into bottom sediments, where sediment-dwelling organisms would be exposed to the substance. However, no environmental monitoring data or toxicity data specific to sediment-dwelling organisms are available for this substance. For this substance, a risk quotient based on exposure in sediment pore water may be calculated based on the aquatic compartment predicted environmental concentration (PEC) and predicted no-effects concentration (PNEC). In the calculation, bottom sediment and its pore water are assumed to be in equilibrium with the overlying water, and benthic and pelagic organisms are assumed to have similar sensitivities to the substance. Therefore the PEC and PNEC for pore water is considered to be the same as for the aquatic compartment. This equilibrium approach would result in a risk quotient (PEC/PNEC) for the sediment compartment that is the same as for the aquatic compartment.

Given that the risk quotient estimates incorporate several conservative assumptions (e.g., mass used was at high end of possible range, low flow conditions in receiving water bodies, no removal by STPs [MegaFlush only]), they overestimate actual risks. These results therefore indicate that neither industrial nor down-the-drain consumer releases of Pigment Red 181 are expected to harm pelagic or benthic aquatic organisms.

**Uncertainties in Evaluation of Ecological Risk**

There is uncertainty respecting the octanol-water partition coefficient with model estimated log $K_{ow}$ values up to 5.92. In this assessment, a more representative log $C_o/C_w$ of 2.06 based on the ratio of the experimentally measured solubility of Pigment Red 181 in n-octanol and in water is used in place of the log $K_{ow}$,. This log $C_o/C_w$ estimate was used as experimental input in a number of models to estimate bioaccumulation potential and toxicity to aquatic organisms when permitted by the model.

There is uncertainty with respect to the toxicity of Pigment Red 181 to aquatic organisms due to a lack of empirical data available for the substance or for close structural analogues. Therefore, ECOSAR aquatic toxicity predictions used to fill this data gap are calculated using the more realistic log ($C_o/C_w$) calculated using experimental data instead

of a modeled log $K_{ow}$. Predicted toxicity values that exceed the solubility of the chemical in water by up to a factor of 10 are considered acceptable in this assessment. Since ECOSAR toxicity estimates for Pigment Red 181 are several orders of magnitude above the solubility of the substance and not pigments are contained in the model training sets, the highly protective TOPKAT fish toxicity value of 0.0786 mg/L was used to calculate the PNEC. It is noted that this TOPKAT prediction is within the Optimum Prediction Space limits of the model but the result is still above the measured water solubility of the substance.

Based on the predicted partitioning behaviour of this chemical, the significance of sediment as an important medium of exposure is not well addressed by the effects data available. Indeed, the effects data identified apply solely to pelagic aquatic exposures, although the water column may not be the only medium of concern based on substances fate characteristics.

# Potential to Cause Harm to Human Health

## Exposure Assessment

As mentioned previously (see Releases to the Environment section), due to its potential industrial and consumer uses, the majority of Pigment Red 181 will be released to water. As no monitoring studies have been identified regarding Pigment Red 181 concentrations in environmental media, these concentrations were modelled using ChemCAN version 6.00 software (ChemCAN 2003). Industry data reported under section 71 of CEPA 1999 and Mass Flow Tool analysis (see Releases to the Environment section) were used to model air, water, soil and sediment concentrations. Predicted concentrations in environmental media were modelled (air: 0.257 ng/$m^3$, water: 0.245 ng/L, and soil and sediment: 0.750 ng/g and 47.4 ng/g) and these levels are considered to result in negligible exposure to the general population.

Pigment Red 181 is a pigment for specialized plastics and various cosmetic products (Herbst and Hunger 2004). Use of cosmetics, including some personal care products could result in direct exposure and therefore is considered to be the predominant source of exposure for the general population of Canada. As previously mentioned, search of the Cosmetics Notification System identified Pigment Red 181 in approximately 2000 products (CNS 2009). Analysis of the product profile showed that approximately 98% of products contained Pigment Red 181 at or below 10%. Maximum concentration in the reported concentration range for each product type was used to estimate exposure to Pigment Red 181 in cosmetic products using ConsExpo version 4.1 (ConsExpo 2006). Dermal contact would be the predominant route of application for most products, except for lipstick and toothpaste. Since Pigment Red 181 is a substance with negligible volatility, exposure via the inhalation route was not estimated. A literature review revealed no information on dermal or oral absorption of this substance.

Products were segregated according to frequency of use, and chronic and acute exposure estimates were calculated (See Appendix III). For frequently used products an aggregated daily oral exposure of 0.08 mg/kg-bw per day was estimated. This was based on potential oral exposure from use of lipstick (0.06 mg/kg-bw per day) and from use of toothpaste (0.02 mg/kg-bw per day). An aggregated daily dermal exposure of 3.9 mg/kg-bw per day was estimated from use of products such as skin moisturizer, antiwrinkle products, face makeup and skin cleanser. Of these products, skin moisturizer was the predominant source of dermal exposure to Pigment Red 181, contributing to approximately 60% of the total aggregated dermal exposure. As it was assumed that all products were used on the same day, these estimates are considered to be upper-bounding. For less frequently used products such as hair dyes and bleaches, acute exposures of 1.4 and 2.8 mg/kg-bw were estimated as applied doses, respectively.

Confidence in the exposure estimates is considered to be low to moderate. Some uncertainties are associated with the concentrations of Pigment Red 181 in environmental media and in cosmetic products in Canada. However use of maximal concentrations in

the reported concentration ranges and the assumption that all frequent use products will be used on the same day provide confidence that estimates of exposure are conservative and upper-bounding.

**Health Effects Assessment**

There were limited hazard data identified in the open literature for Pigment Red 181. However, as part of the petition for listing this substance for use in the United States as a colorant in drugs and cosmetics (D&C Red No. 30[2]), the U.S. FDA conducted an evaluation of multiple submitted animal toxicity studies (US FDA 1982a). As the full U.S. FDA evaluation of these data was not readily available and original toxicity studies are unpublished, a brief summary is provided here as reported in the Federal Register (US FDA 1982a). As part of the petition for listing (CAP 7C0058), the Cosmetic, Toiletry and Fragrance Association (CTFA) submitted relevant data to the U.S. FDA, including two chronic studies in Sprague-Dawley rats and CD-1 mice that were administered Pigment Red 181 over their lifetime via diet at concentrations up to 2% and 5% respectively. These chronic studies were considered to have been conducted according to acceptable standards by the U.S. FDA in terms of study design, number of animals, reporting, etc., and were considered to take precedent over older studies previously submitted as part of the petition for use. Based on evaluation of the more recent toxicity studies, the U.S. FDA concluded that Pigment Red 181 is not carcinogenic and derived an ADI (acceptable daily intake) of 1.25 mg/kg-bw per day for the non-cancer effects observed in these studies[3] (US FDA 1982a).

The limited empirical hazard data identified in the published literature for Pigment Red 181 are summarized briefly below.

No mutagenic effects of Pigment Red 181 were observed in two bacteria mutation assays. Pigment Red 181 was tested in the salmonella/mammalian microsome assay with 5 basic tester strains (TA1535, TA100, TA1537, TA1538, TA98) at concentrations of 50, 100, 500 and 1000 μg/plate, with or without rat liver S9. No mutagenic effects of the chemical were observed (Brown et al. 1979). Muzzall and Cook (1979) conducted a similar mutation test on Pigment Red 181. No mutagenicity of the product containing the chemical was observed on either two frame-shift histidine mutants (TA1537 and TA98) or two base-pair substituted histidine mutants (TA1535 and TA100) at concentrations of 165, 1650 and 3300 μg/plate.

[2] Although Pigment Red 181 is cited as D&C Red No. 30 by the U.S. FDA, for the purposes of this assessment, reference to the U.S. FDA evaluation of this substance will use Pigment Red 181.

[3] The Federal Register entry (US FDA 1982a) did not specifically provide details on the doses tested, the NOEL/LOEL, or the associated effects observed. However, details of the U.S. FDA evaluation process for other colorants (Lipman 1995; US FDA 1982b) indicate that a default safety factor of 100 is used to derive the ADI from the chronic study NOEL. Therefore, the ADI of 1.25 mg/kg-bw/day is assumed to be derived from a NOEL of 125mg/kg-bw/day.

In a developmental toxicity study, rats and rabbits were exposed to Pigment Red 181 by gavage during organogenesis, at doses based on the highest NOEL in rats and dogs in previous two-year feeding studies (actual levels not provided, abstract only). Although limited details are provided for this study, there were no reported treatment-related structural malformations, skeletal effects, or soft-tissue abnormalities in the fetuses (Burnett et al. 1974; also cited in Schardein 1993).

A review article on dye sensitization cited limited details on a study in which numerous cases of eczema were attributed to the exposure of Pigment Red 181 in a manufacturing setting and cases diminished with adequate ventilation. No other details were provided for this study (Cywie et al. 1977, cited in Feinman and Doyle 1988).

The confidence in the toxicity database is lowered due to the limited empirical data available from the open literature. However, a review of multiple unpublished toxicity studies by another regulatory body, the details of which are not available at this time, increases confidence in the hazard data set for this substance.

**Characterization of Risk to Human Health**

In chronic dietary studies in mice and rats for Pigment Red 181, the U.S. FDA concluded that no carcinogenic effects were observed. This substance was also negative for mutagenicity in bacterial assays.

The principal source of exposure to Pigment Red 181 is considered to be through the use of personal care products containing this substance. The upper-bounding aggregate chronic oral exposure from daily use of lipstick and toothpaste was estimated to be 0.08 mg/kg-bw per day, which is well below the oral-based ADI (1.25 mg/kg-bw per day) established by the U.S. FDA (US FDA 1982a).

While the upper-bounding aggregate for chronic dermal exposure to Pigment Red 181 from the use of multiple products on the same day was estimated to be 3.8 mg/kg-bw per day of the applied dose, most of the contribution is due to exposure to skin moisturizer. Occasional use of other products can result in higher acute dermal exposures. However, given that the health effects database for Pigment Red 181 does not indicate that this substance is of high hazard, and that the physical and chemical properties (i.e., high $K_{ow}$) indicate limited potential for dermal absorption, exposures via the dermal route were not considered to be of concern for human health.

**Uncertainties in Evaluation of Risk to Human Health**

While none of the published studies evaluated by the U.S. FDA were critically reviewed by Health Canada for the purposes of this assessment, the study results were extracted from reputable secondary reviews (i.e. US FDA). Other uncertainties are due to the limited additional hazard data identified from the scientific literature for this substance.

There is uncertainty associated with limited information available with respect to the concentrations of Pigment Red 181 in environmental media. Uncertainty is also high with respect to the extent of exposure to Pigment Red 181 from cosmetics and personal care products. However, as all information associated with Pigment Red 181 in the CNS database was considered in the derivation of exposure estimates from use of cosmetics and personal care products, the confidence is high that the derived exposure estimates are very conservative. In addition, maximum concentration in the reported concentration range was used to derive the exposure estimates, also providing confidence that the estimates of exposure are conservative. However additional information on the actual concentration of Pigment Red 181 in cosmetics and personal care products would further refine the exposure characterization.

Some uncertainty is associated with the potential exposure to Pigment Red 181 from pharmaceutical drugs, natural health products and veterinary drugs, which would contribute to oral exposure.

## Conclusion

Based on the information presented in this screening assessment, it is concluded that Pigment Red 181 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 Pigment Red 181 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 Pigment Red 181 does not meet any of the criteria set out in section 64 of CEPA 1999. Additionally, Pigment Red 181 meets the criteria for persistence in water, sediment and soil, but does not meet the criteria for bioaccumulation potential as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

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 I – Robust Study Summary

## A: Evaluation of experimental data using Kollig's approach*

| Item | Weight | Response | Specify | Mark |
|---|---|---|---|---|
| **Reference**: 13365Submission030, Determination of the solubility in water and in octanol of pure Pigment Red 181. | | | | |
| **Test substance**: CAS RN: **2379-74-0, Pigment Red 181** | | | | |
| Could you repeat the experiment with available information? | 5 | Yes | | 5 |
| Is a clear objective stated? | 1 | Yes | | 1 |
| Is water quality characterized or identified (distilled or deionized)? | 2 | Yes | Bi-distilled | 2 |
| Are the results presented in detail, clearly and understandably? | 3 | Yes | | 3 |
| Are the data from a primary source and not from a referenced article? | 3 | Yes | | 3 |
| Was the chemical tested at concentrations below its water solubility? | 5 | N/A | | |
| Were particulates absent? | 2 | Yes | | 2 |
| Was a reference chemical of known constant tested? | 3 | No | | 0 |
| Were other fate processes considered? | 5 | N/A | | |
| Was a control (blank) run? | 3 | N/A | | |
| Was temperature kept constant? | 5 | Yes | | 5 |
| Was the experiment done near room temperature (15–30°C)? | 3 | Yes | 22–23°C | 3 |
| Is the purity of the test chemical reported (> 98%)? | 3 | Yes | "Purified" | 3 |
| Was the chemical's identity proven? | 3 | Yes | | 3 |
| Is the source of the chemical reported? | 1 | No | | 0 |
| **Results:** (X±SE) | Solubility in water = 0.0046 mg/L | | | |
| | Solubility in octanol = 0.53 mg/L | | | |
| **Score:** | 30/34=88% | | | |
| **Degree of reliability**** | High | | | |
| **Comments** | | | | |

* Kollig HP. 1988. Criteria for evaluating the reliability of literature data on environmental process constants. Toxicol Environ Chem 17:287–311.

** The reliability code for ecotoxicological studies of DSL categorization is used.

# Appendix II – PBT Model Inputs Summary Table

| | **Phys-Chem/Fate** | **Fate** | **Fate** | **PBT Profiling** | **Ecotoxicity** |
|---|---|---|---|---|---|
| **Model input parameters** | EPIWIN Suite (all models, including: AOPWIN, KOCWIN, BCFWIN BIOWIN and ECOSAR) | STP (1) ASTreat (2) SimpleTreat (3) (required inputs are different depending on model) | Arnot-Gobas BCF/BAF Model | Canadian-POPs (including: Catabol, BCF Mitigating Factors Model, OASIS Toxicity Model) | Artificial Intelligence Expert System (AIES)/ TOPKAT/ ASTER |
| **SMILES code** | O=C(c(c(S1)cc(c2)Cl)c2C)C1=C(Sc(c3c(cc4Cl)C)c4)C3=O | | | O=C(c(c(S1)cc(c2)Cl)c2C)C1=C(Sc(c3c(cc4Cl)C)c4)C3=O | O=C(c(c(S1)cc(c2)Cl)c2C)C1=C(Sc(c3c(cc4Cl)C)c4)C3=O |
| **Molecular weight (g/mol)** | | 393.31 (1, 2, 3) | | | |
| **Melting point (ºC)** | | | | | |
| **Boiling point (ºC)** | | | | | |
| **Data temperature (ºC)** | | | | | |
| **Density (kg/m$^3$)** | | 1.8336 (2) | | | |
| **Vapour pressure (Pa)** | | 1.1E–8 (1, 3) | | | |
| **Henry's Law constant (Pa·m$^3$/mol)** | | 3.1E–8 (3) | | | |
| **Log $K_{aw}$ (Air-water partition coefficient) (dimensionless)** | | | | | |
| **Log $C_o/C_w$ (Concentration in octanol - concentration in water coefficient) (dimensionless)** | | 2.07 (1) | 2.06 | | |
| **$K_{ow}$ (Octanol-water partition** | | 1.2E+2 (2, 3) | | | |

| | | | | | |
|---|---|---|---|---|---|
| **coefficient) (dimensionless)** | | | | | |
| **Log $K_{oc}$ (Organic carbon-water partition coefficient – L/kg)** | | | | | |
| **Water solubility (mg/L)** | | 4.6E+3 (1, 3) | | | |
| **Log $K_{oa}$ (Octanol-air partition coefficient) (dimensionless)** | | | | | |
| **Soil-water partition coefficient (L/kg)[1]** | | | | | |
| **Sediment-water partition coefficient (L/kg)[1]** | | | | | |
| **Suspended particles-water partition coefficient (L/kg)[1]** | | 2.2E+2 (2) | | | |
| **Fish-water partition coefficient (L/kg)[2]** | | | | | |
| **Aerosol-water partition coefficient (dimensionless)[3]** | | | | | |
| **Vegetation-water partition coefficient (dimensionless)[1]** | | | | | |
| **Enthalpy ($K_{ow}$)** | | | | | |
| **Enthalpy ($K_{aw}$)** | | | | | |
| **Half-life in air (days)** | | | | | |
| **Half-life in water (days)** | | | | | |
| **Half-life in sediment (days)** | | | | | |
| **Half-life in soil (days)** | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| **Half-life in vegetation (days)[4]** | | | | | |
| **Metabolic rate constant (1/days)** | | | | | |
| **Biodegradation rate constant (1/days) or (1/hr) -specify** | | 0.0590 (3, 1/hr) 1.42 (2, 1/days) | | | |
| **Biodegradation half-life in primary clarifier ($t_{1/2\text{-}p}$) (hr)** | | 117.46 (1) | | | |
| **Biodegradation half-life in aeration vessel ($t_{1/2\text{-}s}$) (hr)** | | 11.75 (1) | | | |
| **Biodegradation half-life in settling tank ($t_{1/2\text{-}s}$) (hr)** | | 11.75 (1) | | | |

[1] derived from log $K_{oc}$
[2] derived from BCF data
[3] default value
[4] derived from half-life in water

# Appendix III – Upper-bounding Estimates of Chronic and Acute Intake of Pigment Red 181 from Personal Care Products

## (Parameters used are listed in Appendix IV)

| Product | Concentration (%) | Dermal | Oral |
|---|---|---|---|
| Chronic Exposure (mg/kg per day) | | | |
| Lipstick | 10 | - | 0.06 |
| Toothpaste | 1 | - | 0.02 |
| Skin moisturizer | 1 | 2.26 | - |
| Antiwrinkle preparation | 3 | 0.68 | - |
| Face makeup | 10 | 0.28 | - |
| Skin cleanser | 3 | 0.24 | - |
| Hair conditioner | 0.30 | 0.15 | - |
| Hair grooming | 0.10 | 0.04 | - |
| Eye makeup | 10 | 0.03 | - |
| Manicure preparation | 10 | 0.03 | - |
| Barrier cream | 0.10 | 0.03 | - |
| Fragrance | 0.10 | 0.03 | - |
| Hair shampoo | 0.10 | 0.02 | - |
| Bath preparation | 1 | 0.01 | - |
| Deodorant | 0.10 | 0.01 | - |
| Shaving preparation | 0.10 | $2.8 \times 10^{-3}$ | - |
| **Total chronic** | | **3.80** | **0.08** |
| Acute Exposure (mg/kg per event) | | | |
| Hair dye | 1 | 1.41 | - |
| Hair bleach | 1 | 2.82 | - |

Pigment Red 181 concentrations based on Cosmetic Notification System search (CNS 2009). Dermal oral absorption assumed to be 100%. All scenarios based on ConsExpo 4.1 scenarios (ConsExpo 2006).

# Appendix IV – Parameters Used to Predict Pigment Red 181 exposure from Personal Care Products

| Type of product | Assumptions from RIVM (2006), unless otherwise specified |
|---|---|
| Antiwrinkle cream | Exposure frequency: 730/year<br>Exposed area: 638 $cm^2$<br>Applied amount: 0.8 g |
| Barrier cream | Exposure frequency: 75/year<br>Exposed area: 18 200 $cm^2$<br>Applied amount: 10 g |
| Bath preparation (showering gel) | Exposure frequency: 329/year<br>Exposed area: 18 200 $cm^2$<br>Applied amount: 8.7 g<br>Retention factor: 1% |
| Deodorant (stick) | Exposure frequency: 365/year<br>Exposed area: 100 $cm^2$<br>Applied amount: 0.5 g |
| Eye makeup (eye shadow) | Exposure frequency: 730/year<br>Exposed area: 24 $cm^2$<br>Applied amount: 0.01 g |
| Face makeup (blush) | Exposure frequency: 365/year<br>Exposed area: 160 $cm^2$ (surface area was estimated as 1/8 of total head surface)<br>Applied amount: 0.2 g |
| Fragrance | Exposure frequency: 1095/year<br>Exposed area: 200 $cm^2$<br>Applied amount: 0.61 g |
| Hair conditioner (leave on) | Exposure frequency: 102/year [1]<br>Exposed area: 1550 $cm^2$<br>Applied amount: 12.4 g [1] |
| Hair grooming (gel) | Exposure frequency: 365/year<br>Exposed area: 1090 $cm^2$<br>Applied amount: 2.9 g |
| Hair shampoo | Exposure frequency: 260/year<br>Exposed area: 1550 $cm^2$<br>Applied amount: 20 g<br>Retention factor: 10% |
| Lipstick | Exposure frequency: 1460/year<br>Ingested amount: 0.01 g |
| Makeup (foundation) | Exposure frequency: 365/year<br>Exposed area: 638 $cm^2$<br>Applied amount: 0.8 g |
| Moisturizer (body) | Exposure frequency: 730/year<br>Exposed area: 18 200 $cm^2$<br>Applied amount: 8 g |

| **Type of product** | **Assumptions from RIVM (2006), unless otherwise specified** |
|---|---|
| Nail polish | Exposure frequency: 156/year<br>Exposed area: 4 $cm^2$<br>Applied amount: 0.05 g |
| Skin cleanser (peel-off face pack) | Exposure frequency: 104/year<br>Exposed area: 638 $cm^2$<br>Applied amount: 20 g |
| Shaving cream | Exposure frequency: 365/year<br>Exposed area: 319 $cm^2$<br>Applied amount: 2 g<br>10% retention factor applied. |
| Toothpaste | Exposure frequency: 730/year<br>Ingested amount: 0.08 g |
| Hair bleach | Exposure frequency: 10/year<br>Exposed area: 638 $cm^2$<br>Applied amount: 200 g<br>Retention factor: 10% |
| Hair dye | Exposure frequency: 10/year<br>Exposed area:638 $cm^2$<br>Applied amount: 100 g<br>Retention factor: 10% |

All scenarios assume 100% dermal and oral uptake. Surface areas and body weight (70.9 kg) were referenced from Health Canada (1995).

[1] New Substances Assessment and Control Bureau. 2006 Cosmetics Exposure Workbook. EAU / NSACB - Health Canada (personal communication).