

**Screening Assessment for the Challenge**

**Methanone, bis[4-(dimethylamino)phenyl]-  
(Michler's ketone)**

**Chemical Abstracts Service Registry Number  
90-94-8**

**Environment Canada  
Health Canada**

**March 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 of methanone, bis[4-(dimethylamino)phenyl]- (Michler's ketone), Chemical Abstracts Service Registry Number 90-94-8. The substance Michler's ketone was identified in the categorization of the Domestic Substances List as a high priority for action under the Ministerial Challenge. Michler's ketone was identified as a high priority as it was considered to pose intermediate potential for exposure of individuals in Canada and is classified by the European Commission and the US National Toxicology Program on the basis of carcinogenicity. The substance met the ecological categorization criteria for persistence, but did not meet the ecological criteria for bioaccumulation potential or inherent toxicity to aquatic organisms. Therefore, the focus of this assessment of Michler's ketone relates primarily to human health risks.

Michler's ketone is an organic substance that is found in Canada and elsewhere primarily as a residual in colourants resulting from an intermediary reaction during manufacturing and in final consumer products. Approximately 800 kg of Michler's ketone were imported into Canada in 2006, whereas no manufacturing was reported in Canada for that year. Between 1000 and 10 000 kg of Michler's ketone were used in Canada in 2006. In Canada, most Michler's ketone is used in paper products; minor uses include its industrial use in dry films and in electronics manufacturing.

The quantities and types of uses of Michler's ketone imported into and used in Canada suggest that it could be released into the Canadian environment. Exposures of the general population to Michler's ketone through environmental media are estimated to be negligible. Based upon the information obtained on current uses of Michler's ketone in Canada, exposure of the general population is expected to be very low and limited to the use of paper products containing the chemical as a manufacturing residual in paper colourants. The general population is unlikely to be exposed to Michler's ketone from other consumer products.

Based principally on the weight of evidence-based assessments of international or other national agencies, a critical effect for the characterization of risk to human health for Michler's ketone is carcinogenicity. In standard 2-year carcinogenicity studies with rats and mice exposed orally to Michler's ketone in the diet, increased incidences of hepatocellular carcinomas were observed in male and female rats and female mice, and increased incidences of hemangiosarcomas were observed in male mice. Michler's ketone was genotoxic in a range of *in vivo* and *in vitro* assays. In addition, Michler's ketone bound to liver deoxyribonucleic acid (DNA) and caused liver DNA damage in experimental animals. Although the modes of induction of tumours by Michler's ketone have not been developed and elucidated, the tumours observed in the experimental animals are considered to have resulted from direct interaction with genetic material.

The non-cancer critical effect for characterization of risk to human health for Michler's ketone is reduced body weight gain. However, tumours were observed at the lowest-observed-adverse-effect level (LOAEL) identified for the non-cancer endpoint. Thus, margins of exposure are not derived for this substance.

On the basis of the carcinogenic potential of Michler's ketone, for which there may be a probability of harm at any exposure level, and the evidence that tumours are observed at the lowest doses tested, it is concluded that Michler's ketone is a substance that may be 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 its physical and chemical properties, Michler's ketone is expected to be persistent in water, soil and sediment but is not expected to be persistent in air and is not expected to bioaccumulate in the environment. The substance therefore meets the persistence criteria but does not meet the bioaccumulation criteria as set out in the *Persistence and Bioaccumulation Regulations*. In addition, model data suggest that the substance may have a moderate to high potential for acute toxicity to aquatic organisms. Based on a comparison of predicted no-effect concentrations and estimated reasonable worst-case environmental exposure concentrations, it is concluded that Michler's ketone 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.

Where relevant, research and monitoring will support verification of assumptions used during the screening assessment and, where appropriate, the performance of potential control measures identified during the risk management phase.

Based on the information available, it is concluded that Michler's ketone meets one or more of the criteria set out in section 64 of CEPA 1999.

## 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 Michler's ketone was identified as a high priority for assessment of human health risk because it was considered to present IPE and has been classified by other agencies on the basis of carcinogenicity. The Challenge for this substance was published in the *Canada Gazette* on August 30, 2008 (Canada 2008). 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 uses of the substance were received.

Although Michler's ketone was determined to be a high priority for assessment with respect to human health and it also met the ecological categorization criteria for persistence, it did not meet the criteria for bioaccumulation potential or inherent toxicity to aquatic organisms.

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.

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 May 2009 for the human exposure, human health effects and ecological sections of the document and up to February 2009 for physical and chemical properties, ecological exposure and effects. 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 exposure (non-occupational) 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 prioritizing 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 scientific experts selected and directed by Toxicology Excellence for Risk Assessment (TERA), including Dr. Lynne Haber (Toxicology Excellence for Risk Assessment), Dr. Pam Williams (E Risk Sciences) and Dr. Harlee Strauss (Strauss Associates).

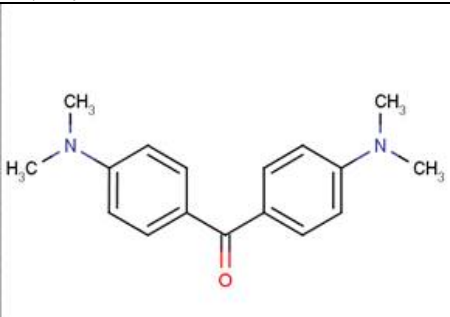
Additionally, the draft of this screening assessment was subject to a 60-day public comment period. While external comments were taken into consideration, the final content and outcome of the screening assessment remain the responsibility of Health Canada and Environment Canada.

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

## Substance Identity

For the purposes of this document, this substance will be referred to as Michler's ketone, a common name for this substance (Table 1).

**Table 1. Substance identity for Michler's ketone**

<b>CAS RN</b>	90-94-8
<b>DSL name</b>	Methanone, bis[4-(dimethylamino)phenyl]-
<b>NCI names</b>	Benzophenone, 4,4'-bis(dimethylamino)- (PICCS) 4,4'-Bis(dimethylamino)benzophenone (ECL, EINECS) 4,4'-Bis (dimethylamino) benzophenone (ENCS) Methanone, bis[4-(dimethylamino)phenyl]- (AICS, ASIA-PAC, DSL, NZIoC, PICCS, TSCA)
<b>Other names</b>	4,4'-Bis(N,N-dimethylamino)benzophenone; p,p'-Bis(dimethylamino)benzophenone; Bis(4-dimethylaminophenyl) ketone; Bis[p-(N,N-dimethylamino)phenyl] ketone; Bis[(4-dimethylamino)phenyl]methanone; DABP; Di(p-dimethylamino)benzophenone; Michler's ketone; Nisso Cure MABP; NSC 9602; S 112; S 112 (ketone); 4,4'-Tetramethyldiaminobenzophenone; N,N,N',N'-Tetramethyl-4,4'-diaminobenzophenone; p,p'-Tetramethyldiaminobenzophenone
<b>Chemical group (DSL stream)</b>	Discrete organics
<b>Major chemical class or use</b>	Ketones
<b>Major chemical subclass</b>	Benzophenones
<b>Chemical formula</b>	C <sub>17</sub> H <sub>20</sub> N <sub>2</sub> O
<b>Chemical structure</b>	
<b>SMILES</b>	O=C(c(ccc(N(C)C)c1)c1)c(ccc(N(C)C)c2)c2
<b>Molecular mass</b>	268.36 g/mol

Abbreviations: AICS, Australian Inventory of Chemical Substances; ASIA-PAC, Asia-Pacific Substances Lists; CAS RN, Chemical Abstracts Service Registry Number; DSL, Domestic Substances List; ECL, Korean Existing Chemicals List; EINECS, European Inventory of Existing Commercial Chemical Substances; ENCS, Japanese Existing and New Chemical Substances; NCI, National Chemical Inventories; NZIoC, New Zealand Inventory of Chemicals; PICCS, Philippine Inventory of Chemicals and Chemical Substances; SMILES, simplified molecular input line entry specification; TSCA, Toxic Substances Control Act Chemical Substance Inventory.

Source: NCI 2006

## Physical and Chemical Properties

Table 2 contains experimental and modelled physical and chemical properties of Michler's ketone that are relevant to its environmental fate.

**Table 2. Physical and chemical properties of the neutral form of Michler's ketone**

Property	Type	Value <sup>1</sup>	Temperature (°C)	Reference
Melting point (°C)	Experimental	179.0		PhysProp 2006
	Modelled	128.7		MPBPWIN 2008
Boiling point (°C)	Modelled	373.9 <sup>2</sup>		MPBPWIN 2008
Vapour pressure (Pa)	Experimental	$2.8 \times 10^{-4}$ ( $2.1 \times 10^{-6}$ mmHg)		GEMS 1987
	Modelled	$1.2 \times 10^{-4}$ ( $8.9 \times 10^{-7}$ mmHg)	25	MPBPWIN 2008
Henry's Law constant (Pa·m <sup>3</sup> /mol)	Experimental	$5.7 \times 10^{-7}$ ( $5.6 \times 10^{-12}$ atm·m <sup>3</sup> /mol)		Hine and Mookerjee 1975
	Modelled	$5.0 \times 10^{-5}$ ( $4.9 \times 10^{-10}$ atm·m <sup>3</sup> /mol)	25	HENRYWIN 2008
Log K <sub>ow</sub> (dimensionless)	Experimental	3.9		Hansch et al. 1995
	Modelled	3.5		KOWWIN 2008
Log K <sub>oc</sub> (dimensionless)	Modelled	2.5 <sup>3</sup>		PCKOCWIN 2009
Water solubility (mg/L)	Experimental	Practically insoluble <sup>4</sup>	20	Merck 2006
	Modelled	1.4	25	WSKOWWIN 2008
pK <sub>a</sub> (dimensionless)	Modelled	2.6 (base form)		ACD/pK <sub>a</sub> DB 2005

Abbreviations: K<sub>oc</sub>, organic carbon-water partition coefficient; K<sub>ow</sub>, octanol-water partition coefficient; pK<sub>a</sub>, acid dissociation constant.

<sup>1</sup> Values in parentheses represent the original values reported by the authors or estimated by the models.

<sup>2</sup> Michler's ketone will decompose above 360°C (Merck 2006).

<sup>3</sup> Molecular connectivity index (MCI) method used.

<sup>4</sup> There is uncertainty about the experimental water solubility. A value of 400 mg/L was found in the EPISuite 2009 database, however the original experiment was carried out many years ago (Dehn 1917) and the value is more than two orders of magnitude greater than the modelled value.

The models based on quantitative structure–activity relationships (QSAR) were used to generate data for some of the physical and chemical properties of Michler's ketone. These models (except for WSKOWWIN 2008) are mainly based on fragment addition methods—that is, they rely on the structure of a chemical. Since these models only accept the neutral form of a chemical as input (in SMILES form), the modelled values shown in Table 2 are for the neutral form of Michler's ketone. Under the environmentally relevant pH's of 6-9, Michler's ketone is neutral in water and is considered non-ionizing. The

substance ionizes in water as a base. Its primary acid dissociation constant is predicted to be  $pK_{a1} = 2.55$  and the secondary acid dissociation constant  $pK_{a2} = 1.11$  by the modelling program pKa dB from ACD (2005). Since the secondary acid dissociation constant  $pK_{a2} = 1.11$  is much less than 5, the base form  $LH^+$  will prevail over the acid form  $LH_2^{2+}$ . Similarly, the primary acid dissociation constant  $pK_{a1} = 2.55$  is much less than 5, which indicates that the base form L will prevail over the acid form  $LH^+$ . Overall, the neutral form L will prevail over the ionic forms  $LH^+$  and  $LH_2^{2+}$ .

## Sources

Michler's ketone is an anthropogenic substance and does not occur naturally in the environment. It can be made by condensing dimethylaniline with phosgene in the presence of zinc chloride (Gessner and Mayer 2000; Röper et al. 2000). Another method of production uses dimethylaniline, aluminum chloride and carbon tetrachloride (Merck 2006; Lewis 2007; HSDB 2009). An alternative method involves the catalytic oxidation of bis(dimethylaminophenyl) methane (Gessner and Mayer 2000). Michler's ketone is a major degradation product of the dye crystal violet. It can also be demethylated to [N,N-dimethylaminophenyl] [N-methylaminophenyl] benzophenone (Chen et al. 2008).

Based on information collected through a survey conducted pursuant to section 71 of CEPA 1999, approximately 800 kg of Michler's ketone were imported into Canada in 2006, and no manufacturing was reported in that year (Environment Canada 2008).

Previously received information from the Domestic Substances List (DSL) nomination (1984–1986) showed that the total quantity of Michler's ketone reported as imported, manufactured or in commerce in Canada during the calendar year 1986 was 1 000 000 kg (Environment Canada 1988). Therefore, Michler's ketone production, import and use in Canada have decreased significantly since the 1980s. Michler's ketone has been identified by the European Union as a low production volume chemical (ESIS 2009).

## Uses

According to submissions made under section 71 of CEPA 1999 and the Challenge questionnaire submissions (Environment Canada 2008), between 1 000 to 10 000 kilograms of Michler's ketone were used in Canada in 2006.

The majority of Michler's ketone used in Canada may be found as a residue in paper colourant (i.e., dye, pigment, stain, ink) at a concentration of 0.009–4.5% by weight (primarily  $\leq 1\%$ ). Michler's ketone is present as a residual in dyes and pigments resulting from an intermediary reaction during manufacturing. It could be present in industries involved in manufacturing paper or converting manufactured paper into different forms, such as paper mills or newsprint mills (Environment Canada 2008). Some examples of paper colourants that may contain residual Michler's ketone include crystal violet, Basazol Violet, Basic Brown C2, Basic Purple 48 and Methyl Violet DAW (Environment Canada 2008). From a literature search, it was found that Michler's ketone may be found



in auramine derivative dyes and pigments (NTP 2005). Auramine dyes can be used to dye paper, textiles and leather, to colour ballpoint pen pastes and inks, and as an antiseptic fungicide (National Cancer Institute 1979; Gessner and Mayer 2000; Thetford 2000; NTP 2005; Merck 2006; Cheminfo 2008; HSDB 2009). The presence of Michler's ketone in pen inks was confirmed in Canada by Health Canada's Consumer Product Safety Directorate. To date, Michler's ketone has not been identified in any children's markers; further testing is ongoing (2010 personal communication from Consumer Product Safety Directorate, Health Canada, to Existing Substances Bureau, Health Canada; unreferenced). The presence of Michler's ketone in textiles was not confirmed in Canada.

Michler's ketone has been used in Canada at a maximum percentage of 0.2% by weight to make Gentian Violet (Harleco), a certified biological stain (MSDS 2004a, 2006a; Environment Canada 2008). It has also been used in the electronics manufacturing industry as a process chemical for circuit board manufacturing at a concentration of 0.24% (Chiang and Kuo 2002; Environment Canada 2008) and as a component in dry film products (at concentrations below 1% by weight).

In Canada, Michler's ketone is not listed in the Drug Products Database, the Natural Health Products Ingredients Database or Licensed Natural Health Products Database. Use of Michler's ketone in therapeutic products was not reported under section 71 of CEPA 1999. Thus, it is not expected that this substance would be present in pharmaceuticals or natural health products manufactured in Canada. However, Michler's ketone may be present in trace amounts in pharmaceuticals imported into Canada, as it is known that uses outside Canada can include its use as a chemical intermediate in the manufacture of pharmaceuticals (Techrainbow 2009; 2009 personal communication from Therapeutic Products Directorate, Health Canada, to Existing Substances Bureau, Health Canada; unreferenced).

In Canada, Michler's ketone is very seldom reported in inks used for food packaging applications (2009 personal communication from Food Directorate, Health Canada, to Existing Substances Bureau, Health Canada; unreferenced). Michler's ketone can be found as a residual in trace amounts in some colour concentrates for paperboard, although there would be no migration to food expected because this application is intended for dry food only. Outside of Canada, Michler's ketone has been reported to be used in ultraviolet (UV)-cured printing inks for cartonboard, acting as a catalyst to harden ink when it is exposed to UV light during the printing process (Castle et al. 1997; Salafranca and Franz 2000). Printing ink is typically applied to the outside of food packaging materials, and therefore there would be no direct contact with food. Today, other aromatic amines (e.g. 4,4'-bis-(diethylamino)-benzophenone (DEAB) and 2-amino-4-methylbenzophenone (AMB)) have replaced Michler's ketone, the use of which is no longer recommended by the printing industry in Japan and Europe (Castle et al. 1997; Nagarajan et al. 2000; Salafranca and Franz 2000).

A number of additional uses of Michler's ketone have been reported outside of Canada. It can be used as a light absorbent (Yasuda et al. 2008), in photoresist formulations (Fan 2004), in polymer production (Emmett et al. 1977; Pillai et al. 1982; Shen et al. 1984;

Tanaka et al. 1993; Granchak et al. 1995; Huang et al. 1999; Onen 2001; Fan 2004) and in chemical production (Dikusar 2003; DTIRP 2004). It can also be used to investigate the polarities of liquid and solid environments (Spange et al. 2002; Zimmermann et al. 2002; Zimmermann and Spange 2002a, b) and as a colour test for nitrites, nitrates and glyceryl trinitration I solutions in distilled water (Munch et al. 1964; Gessner and Mayer 2000; Dikusar 2003).

### Release to the Environment

Based on information collected through a survey conducted pursuant to section 71 of CEPA 1999, one facility involved in colourant production reported releases to air of minimal amounts of Michler's ketone from the blending of custom dye colours. No measurements or emission estimates were compiled by the facility for this substance, as emissions were not considered to be significant. The quantity of dyes blended at the facility has been reduced since 2006. Some other facilities use a sewage treatment system to minimize releases and limit environmental exposure (Environment Canada 2008).

Michler's ketone (and its salts) is reportable to the National Pollutant Release Inventory (NPRI 2008). There were no releases listed under the NPRI. No recent releases were identified in the US Toxics Release Inventory (TRI), as Michler's ketone is no longer tracked, although 182 kg of Michler's ketone in stack air was released in 1997 (TRI 1997). The NPRI and the TRI both address releases to air, water and land. However, medium-specific data were provided only for air.

### Environmental Fate

Based on its physical and chemical properties (Table 2), the results of Level III fugacity modelling (Table 3) suggest that Michler's ketone will reside predominantly in soil if released to air or soil and will remain primarily in water if released to the aquatic environment.

**Table 3. Results of the Level III fugacity modelling (EQC 2003) for Michler's ketone**

Substance released to:	Percentage of substance partitioning into each compartment			
	Air	Water	Soil	Sediment
Air (100%)	0.01	2.00	97.60	0.44
Water (100%)	0.0	82	0.0	18
Soil (100%)	0.0	0.2	99.70	0.05

## Persistence and Bioaccumulation Potential

### Environmental Persistence

No experimental degradation data for Michler's ketone have been identified. Given the ecological importance of the water compartment, the fact that most of the available models apply to water and the fact that Michler's ketone is expected to be released to this compartment, persistence in water was examined primarily using predictive QSAR models for biodegradation.

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

**Table 4. Modelled data for degradation of Michler's ketone**

Fate process	Model and model basis	Model result and prediction	Extrapolated half-life (days)
<b>Air</b>			
Atmospheric oxidation	AOPWIN 2008	$t_{1/2} = 0.052$ day	$\leq 2$
Ozone reaction	AOPWIN 2008	n/a <sup>1</sup>	n/a
<b>Water</b>			
Hydrolysis	HYDROWIN 2008	n/a	n/a
Biodegradation (aerobic)	BIOWIN 2009 Submodel 3: Expert Survey (ultimate biodegradation)	2.1 <sup>2</sup> "biodegrades slowly"	$\leq 182^3$
Biodegradation (aerobic)	BIOWIN 2009 Submodel 4: Expert Survey (primary biodegradation)	2.9 <sup>2</sup> "may biodegrade fast"	$\leq 182$
Biodegradation (aerobic)	BIOWIN 2009 Submodel 5: MITI linear probability	-0.1 <sup>3</sup> "biodegrades very slowly"	$\geq 182$
Biodegradation (aerobic)	BIOWIN 2009 Submodel 6: MITI non-linear probability	0.007 <sup>3</sup> "biodegrades very slowly"	$\geq 182$
Biodegradation (aerobic)	TOPKAT 2004 Probability	0.0 <sup>3</sup> "biodegrades very slowly"	$\geq 182$
Biodegradation (aerobic)	CATABOL ©2004–2008 % BOD	% BOD = 0.10 "biodegrades very slowly"	$\geq 182$

Abbreviations: BOD, biochemical oxygen demand; MITI, Ministry of International Trade & Industry, Japan;  $t_{1/2}$ , half-life.

<sup>1</sup> Model does not provide an estimate for this type of structure.

<sup>2</sup> Output is a numerical score.

<sup>3</sup> Output is a probability score.

In air, a predicted atmospheric oxidation half-life value of 0.052 day (Table 4) 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 ozone, 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 for Michler's ketone in the

atmosphere. With a half-life of 0.052 day via reactions with hydroxyl radicals, Michler's ketone is considered not persistent in air.

In water, a predicted hydrolysis half-life value could not be estimated for the structure of Michler's ketone. However, other fate processes in water need to be considered to determine its overall level of persistence in this medium.

The model results for ultimate biodegradation suggest that Michler's ketone does not biodegrade rapidly. The four ready biodegradation models (BIOWIN Submodels 3, 5 and 6, TOPKAT and CATABOL) predict that ultimate biodegradation is very slow and that the half-life in water would be considerably longer than 182 days. Predictions for CATABOL and TOPKAT are in all the domains of both models and are thus considered to be the most reliable. According to BIOWIN's ready biodegradability prediction, Michler's ketone is not readily biodegradable. The BIOWIN primary survey model predicts that primary degradation may occur relatively fast compared with complete mineralization; however, the identities of the primary degradation products are not known. The substance contains structural features associated with chemicals that are not easily biodegraded (e.g., ketones). Therefore, considering all model results (particularly for ultimate degradation) and structural features, there is sufficient evidence that the biodegradation half-life of Michler's ketone is  $\geq 182$  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  $\geq 182$  days, and the half-life in sediments is  $\geq 365$  days. This indicates that Michler's ketone is expected to be persistent in soil and sediment.

Based on the modelled data (see Table 4), Michler's ketone meets the persistence criteria in water, soil and sediment (half-lives in soil and water  $\geq 182$  days and half-life in sediment  $\geq 365$  days) but does not meet the criterion for air (half-life in air  $\geq 2$  days) as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

### Potential for Bioaccumulation

Low to moderate experimental and modelled log  $K_{ow}$  values for Michler's ketone (see Table 2 above) suggest that this chemical has relatively low potential to bioaccumulate.

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

**Table 5a. Empirical data for bioaccumulation of Michler's ketone**

Test organism	Endpoint	Value (L/kg wet weight)	Reference
Fish ( <i>Cyprinus carpio</i> )	BCF	25–54	MITI 2002

Although experimental BCF data for Michler's ketone were available, a predictive approach was also applied using available bioaccumulation factor (BAF) and BCF models, as shown in Table 5b.

**Table 5b. Fish BAF and BCF predictions for Michler's ketone using the Arnot and Gobas (2003) kinetic model with a default of no metabolism**

Test organism	Log K <sub>ow</sub>	Endpoint	Value (L/kg wet weight)	Reference
Fish	3.87	BAF	83.43 <sup>1</sup>	Arnot and Gobas 2003 (modified Gobas BAF middle trophic level)
Fish	3.87	BCF	83.36 <sup>1</sup>	Arnot and Gobas 2003 (modified Gobas BCF middle trophic level)
Fish	3.5	BCF	25.12	OASIS Forecast 2005
Fish	3.87	BCF	43.18	BCFBAF 2009

<sup>1</sup> The Arnot and Gobas (2003) kinetic model was applied with a default of no metabolism.

According to the *Persistence and Bioaccumulation Regulations* (Canada 2000), a substance is bioaccumulative if its BCF or BAF is  $\geq 5\,000$ ; however, BAF is the preferred metric for assessing the bioaccumulation potential of substances. This is because the BCF may not adequately account for the bioaccumulation potential of substances via the diet, which predominates for substances with  $\log K_{ow} > \sim 4.0$  (Arnot and Gobas 2003). Kinetic mass balance modelling is in principle considered to be the most reliable method for predicting the bioaccumulation potential because it allows for metabolism correction as long as the  $\log K_{ow}$  of the substance is within the  $\log K_{ow}$  domain of the model. However, if the  $\log K_{ow}$  is less than 4.0, as is the case with Michler's ketone, uptake into the fish is mainly via the gills; therefore, metabolism via the gut is not important.

The modified Gobas BAF middle trophic level model for fish predicted a BAF of 83.43 L/kg, indicating that Michler's ketone does not have the potential to significantly bioaccumulate in fish or to biomagnify in food webs. The results of BCF model calculations provide additional evidence supporting the low bioconcentration potential of this substance.

Based on the available empirical and kinetic-based modelled values, Michler's ketone does not meet the bioaccumulation criteria (BCF or BAF  $\geq 5\,000$ ) as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

### Potential to Cause Ecological Harm

The approach taken in this assessment was to examine the available scientific 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 the persistence, bioaccumulation, toxicity, sources and fate of the substance.

As described previously, Michler's ketone has a short half-life in air but is persistent in water, soil and sediment. It is expected to have a low bioaccumulation potential. Experimental ecological effects data are summarized in Table 6a.

**Table 6a: Empirical data for aquatic toxicity of Michler's ketone**

Test organism	Test type	Endpoint	Value (mg/L)	Reference
<i>Daphnia magna</i>	Acute	EC <sub>50</sub>	>100	Study Submission 2005

Abbreviation: EC<sub>50</sub>, the concentration of a substance that is estimated to cause some toxic sublethal effect on 50% of the test organisms.

A study on the acute aquatic toxicity of Michler's ketone to *Daphnia magna* resulted in an EC<sub>50</sub> of >100 mg/L using Organisation for Economic Co-operation and Development (OECD) Test Guideline 202 (Study Submission 2005) (Table 6a). This value suggests that Michler's ketone is of low acute toxicity and is not expected to cause harm to aquatic organisms at relatively low concentrations.

A range of aquatic toxicity values was obtained using QSAR models (Table 6b). The model predictions generally indicated much higher toxicity than the measured result. Most of the modelled toxicity values are within a factor of 10 of the modelled solubility of the substance (1.4 mg/L). The model results are deemed acceptable as they are within the model domain. Overall, the results suggest that Michler's ketone has the potential to cause moderate to high acute toxicity in aquatic organisms.

**Table 6b. Modelled data for aquatic toxicity of Michler's ketone**

Test organism	Log Kow	Type of test	Endpoint	Value (mg/L)	Reference
Fish	3.5	Acute (96 h)	LC <sub>50</sub>	0.89 <sup>1</sup>	TOPKAT 2004
	3.87			9.85	ECOSAR 2009 (neutral organics)
	n/a			4.42	ASTER 1999
	3.5			142	AIES 2003–2005
<i>Daphnia</i>	3.5	Acute (48 h)	EC <sub>50</sub>	3.8	TOPKAT 2004
<i>Daphnia</i>	3.5	Acute (48 h)	EC <sub>50</sub>	7.32	AIES 2003–2005
<i>Daphnia</i>	3.87	Acute (48 h)	EC <sub>50</sub>	6.94	ECOSAR 2009 (neutral organics)
Mysid shrimp	3.87	Acute (96 h)	LC <sub>50</sub>	3.36	ECOSAR 2009 (neutral organics)

Abbreviations: LC<sub>50</sub>, concentration of a substance that is estimated to be lethal to 50% of the test organisms.

<sup>1</sup> – Critical Toxicity Value

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

Michler's ketone is used primarily in industrial applications (see Uses section above); therefore, industrial releases to water may occur. In the absence of environmental monitoring data, a generic scenario was used to estimate a reasonable worst-case concentration of Michler's ketone resulting from an industrial discharge using Environment Canada's Industrial Generic Exposure Tool – Aquatic (IGETA). The predicted environmental concentration (PEC) was estimated based on the maximum quantity used at one facility, the fraction estimated to be discharged to a sewage treatment plant (STP), the STP removal rate, the STP effluent flow and the dilution capacity of the receiving water body (assumed to be small). Key inputs were the fraction

of the substance discharged to the STP (0.3%; Great Western Containers 2005), resulting from the cleaning of semi-bulk containers or totes that are assumed to be used for the transportation of the substance, and the proportion estimated to be removed in the STP (43.7%; Environment Canada 2009). A PEC of 0.0035 mg/L was calculated. Details regarding the inputs used to estimate this concentration and the output of the model are described in Environment Canada (2009).

As the empirical toxicity value is relatively high (>100 mg/L Study Submission 2005) and provides only a lower-bounding value, the conservative QSAR value of 0.89 mg/L, representing the 96-hour median lethal concentration (LC<sub>50</sub>) in fish (TOPKAT 2004), was selected as the critical toxicity value (CTV) for estimating the toxicity of Michler's ketone to sensitive aquatic organisms.

A conservative predicted no-effect concentration (PNEC) was then derived using the CTV of 0.89 mg/L. The CTV was divided by an assessment factor of 100 to account for uncertainties related to interspecies and intraspecies variability in sensitivity and extrapolation from a laboratory LC<sub>50</sub> to a no-effect value in the field. This yielded a PNEC of 0.0089 mg/L.

The resulting conservative risk quotient (PEC/PNEC) of 0.39 indicates that exposures are unlikely to cause harm to aquatic organisms. As indicated in the fate section, most of the substance that is discharged to water and will remain in that compartment. Exposures of organisms in other locations or in media other than water are less likely.

As noted previously, Michler's ketone meets the criteria for persistence in water, soil and sediment but does not meet the criterion for air as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000). In addition, the substance does not meet the bioaccumulation criteria as specified in the Regulations. The available modelled toxicity values indicate that Michler's ketone may have a moderate to high potential to cause acute toxicity in aquatic organisms. However, based on reasonable worst case estimates of exposure and no-effect concentrations, it is considered that Michler's ketone is unlikely to be present in the Canadian environment at concentrations sufficient to cause ecological harm. Therefore, based on the available information, it is concluded that Michler's ketone does not pose a risk to the Canadian environment.

### **Uncertainties in Evaluation of Ecological Risk**

An uncertainty relates to the lack of data on environmental concentrations in Canada, which was addressed by predicting a reasonable worst-case concentration in water using an industrial exposure model. There is also uncertainty associated with the PNEC used in the risk quotient calculation, because of the limited number of empirical toxicity data available, which required reliance on QSAR data. These uncertainties were partly addressed by the assessment factor of 100 that was used when deriving the aquatic PNEC.

There are also uncertainties associated with the use of QSAR models to estimate persistence and bioaccumulation. However because the properties of the substance were within the domains of the models and since the various QSAR models used gave similar results, the conclusions regarding the persistence and bioaccumulation potential of Michler's ketone are considered credible.

## Potential to Cause Harm to Human Health

### Exposure Assessment

Based on the physical and chemical properties of Michler's ketone, the primary routes of exposure are likely to be oral and dermal. A low vapour pressure and low Henry's Law constant indicate that Michler's ketone is non-volatile. The inhalation route of exposure is therefore not likely to be as relevant as the oral and dermal exposure pathways.

### *Environmental Media and Food*

As no monitoring studies have been identified that have measured levels of Michler's ketone in air, water, soil or sediment, in Canada or elsewhere, ChemCAN, a Canadian-specific environmental exposure model, was used to predict concentrations in environmental media based on the amount of the substance used in Canada (ChemCAN 2003). The model predicted very low concentrations of Michler's ketone in these media (ChemCAN 2003). The total volume of Michler's ketone used in Canada (1000–10 000 kg) was used in ChemCAN to approximate Canadian releases. Default parameters were used in the modelling. Upper-bounding estimates of intake of Michler's ketone for various age groups in the general population of Canada, based upon the maximum concentrations in relevant environmental media (air, drinking water, soil) obtained from ChemCAN, were determined. The upper-bounding estimate of daily intake for all age groups of the general Canadian population was <0.01 µg/kg-bw per day.

In Canada, Michler's ketone can be found as a residual in trace amounts in some colour concentrates for paperboard. However, as such applications are intended for dry food only, there would be no expected migration into food. Some studies have also investigated the possibility of Michler's ketone being present as a residue in some food packaging materials that are made from recycled fibres (Castle et al. 1997; Ozaki et al., 2004, 2006). In the 1997 study, the three food samples with the highest measured concentrations of Michler's ketone were analysed by gas chromatography–mass spectrometry after extraction and cleanup. There was no measurable migration of Michler's ketone at a detection limit of 2 µg/kg food (Castle et al. 1997). In a more recent study (Ozaki et al. 2004), very low levels (1.7–12 µg/g) of Michler's ketone were found in recycled paper products only, not in virgin products. In a follow-up study, Ozaki et al. (2006) performed migration studies using food simulant solvents. Migration was observed from paperboard containing recycled fibres when using 95% alcohol, albeit at extremely low levels (<10 ng/ml) (Ozaki et al. 2006). However, because recycled paperboard products for food packaging are used with a protective coating or are used for



pre-packaged foods (i.e., a functional barrier would be present), there would be no direct contact with food. Therefore, there would be no exposure to Michler's ketone from food.

Confidence in the exposure database for environmental media is considered to be low. The majority of the information available is not specific to Canada. Low confidence has been assigned due to inadequate survey or monitoring data or industrial release/emissions data for modelling concentrations in relevant media. The amount of Michler's ketone used in commerce was used to estimate the concentrations in relevant media.

### *Consumer Products*

Although there are a number of industrial uses of Michler's ketone, only a limited number of applications were identified for consumer products, most notably a colourant residue in inks, dyes, pigments and stains (Environment Canada 2008). The most probable exposure of the general population in Canada is from the presence of residual Michler's ketone in colourants in paper products, with lesser contributions from other pigment-containing products.

Residual levels of Michler's ketone may be present in some dyes and final consumer products (Environment Canada 1988; NTP 2005). Michler's ketone can be found as a residue in printing inks or adhesives at concentrations of 0.1–1.6% (MSDS 2000, 2003b, 2004a; Aurela 2001; European Commission 2008); in printer ribbons at concentrations ranging from <0.1% by weight (MSDS 2001a, 2004b, 2006b) to 7.2% (in purple printer ribbon) (MSDS 2007); in nylon fabric ribbon cassettes at <0.30% by weight (MSDS 2004b); in pen ink (at <1% in ball point pens) (Basel-Stadt 2003; MSDS 2003a); and in solvent blue 4 triarylmethane dye at 4.5% (MSDS 2001b).

A conservative consumer product scenario to estimate oral exposure to residual Michler's ketone in paper colourants from possible ingestion of paper by children was conducted (Appendix 1). For 0.5- to 4-year-olds, oral exposure per event was estimated to be  $8 \times 10^{-4}$  mg/kg body weight (kg-bw). The ingestion of paper products is more likely for children 0.5–4 years of age than for infants under 6 months of age or for older populations; however, some mouthing of paper by infants may occur. The potential inhalation and dermal exposures to Michler's ketone from paper products were not modeled due to the lack of available models; however, exposure from these routes is likely very limited due to the physical and chemical properties of Michler's ketone as well as the impregnation of the colourant in the paper.

Additional information on Michler's ketone use in ball pens and marker lines has been reported by Art and Creative Materials Institute (ACMI), Duke University (2009 personal communication to Health Canada; unreferenced). Michler's ketone was only found in ball point pen and permanent marker inks. They have identified Michler's ketone in seven ball point pen inks, used in four pen lines with levels ranging from 0.0023-0.11%. Michler's ketone was also identified in 18 permanent marker inks used in 7 marker lines with levels ranging from 0.00024-0.13%.

Sufficient data were available with which to predict oral and dermal exposure from ball pens, although based on information available on Canadian use patterns, this route of exposure is less likely in Canada (Appendix 2) (Hansen et al. 2008). The estimated conservative per event dermal or oral exposure to ink from the pens was  $4 \times 10^{-3}$  mg/kg-bw in 0.5- to 4-year-olds. Although no information was received from the section 71 survey regarding the presence of Michler's ketone in ink in pens sold in Canada, Michler's ketone use in pen inks has been reported in the literature. In addition, the presence of Michler's ketone in pen inks was confirmed in Canada by Health Canada's Consumer Product Safety Directorate. To date, Michler's ketone has not been identified in any children's markers; further testing is ongoing (2010 personal communication from Consumer Product Safety Directorate, Health Canada, to Existing Substances Bureau, Health Canada; unreferenced).

Based upon the information identified with respect to use, there is low confidence in the modelled estimates from consumer products. There are data on some types of products containing Michler's ketone found in Canada, but chemical-specific parameters needed to estimate exposures to consumer products are limited. Exposure of the general population to Michler's ketone is limited primarily to the use of paper products. However, there is uncertainty with respect to the extent of exposure from this source, as there is limited exposure information available regarding Michler's ketone's presence as a colourant residue in paper products in Canada. There are also limited exposure models available for this scenario. The scenarios are considered upper-bound estimates of exposure, as they are conservative and exposure is considered intermittent in nature.

## Health Effects Assessment

Appendix 3 contains a summary of the available health effects information for Michler's ketone.

The US National Toxicology Program classified Michler's ketone as *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity in experimental animals (National Cancer Institute 1979; NTP 2005). The European Commission classified Michler's ketone as a Carcinogen Category 2 substance (*should be regarded as if they are carcinogenic to man*) with risk phrase R45 (*may cause cancer*) based on tumours observed in rat and mouse livers (European Commission 2002, 2004; ESIS 2009). Additionally, the European Commission classified Michler's ketone as a Mutagen Category 3 substance with risk phrase R68 (*possible risk of irreversible effects*) based on *in vivo* genotoxicity in somatic cells (European Commission 2002, 2004; ESIS 2009). Recently, the International Agency for Research on Cancer classified Michler's ketone as a Group 2B carcinogen (*possibly carcinogenic to humans*) based on the observation of tumours at many sites in rodents (Baan et al. 2008).

When administered orally in the diet, Michler's ketone induced increased incidences of liver tumours in male and female rats and female mice and of blood vessel tumours in male mice. In the National Cancer Institute (1979) carcinogenicity studies, incidences of hepatocellular carcinoma were increased significantly in a dose-related manner in male Fischer 344 rats (0/20, 9/50 and 40/50 for 0, 12.5 and 25 mg/kg-bw per day, respectively;  $p < 0.05$  for the low dose) and in female Fischer 344 rats (0/20, 41/47 and 44/49 for 0, 25 and 50 mg/kg-bw per day, respectively;  $p < 0.01$  for the low dose) after exposure to Michler's ketone in the diet for 78 weeks followed by an observation period of 28 or 29 weeks. The incidences of combined neoplastic lesions (hepatocellular carcinoma and neoplastic nodules) were also increased significantly at both doses in both sexes (National Cancer Institute 1979). Similarly, in the carcinogenicity bioassay with B6C3F1 mice, the incidences of hepatocellular carcinoma were increased significantly in a dose-related manner (0/19, 16/49 and 38/50 for 0, 179 and 357 mg/kg-bw per day, respectively;  $p < 0.01$  for the low dose) in female mice exposed to Michler's ketone in the diet for 78 weeks followed by an observation period of 13 weeks. In male mice, no significantly increased incidences of hepatocellular carcinoma were observed, but a significantly increased incidence of hemangiosarcoma was observed at the high dose (0/19, 5/50 and 20/50 for 0, 179 and 357 mg/kg-bw per day, respectively;  $p < 0.01$  for the high dose) (National Cancer Institute 1979).

Michler's ketone was found to be genotoxic in a number of *in vivo* assays in experimental animals and *in vitro* assays in mammalian cells and some *Salmonella* test strains (Appendix 3). In *in vivo* bioassays, Michler's ketone caused a significant increase in the number of sister chromatid exchanges in the bone marrow of Swiss mice administered Michler's ketone by intraperitoneal injection (Parodi et al. 1982). Michler's ketone was found to bind with the deoxyribonucleic acid (DNA) of the liver or kidney in rats after intraperitoneal injection (Scribner et al. 1980; Struck et al. 1981). In addition, Michler's ketone caused liver DNA damage assessed by the alkaline elution assay in Sprague-

Dawley rats after administration by intraperitoneal injection (Parodi et al. 1982) and by gavage (Kitchin and Brown 1994). It also induced unscheduled DNA synthesis in rats when administered by gavage (Mirsalis et al. 1989). In *in vitro* mammalian cell bioassays, Michler's ketone caused a dose-dependent increase of mutation frequencies in mouse lymphoma L5178Y cells in the presence or absence of induced liver S9 (Mitchell et al. 1988; Myhr and Caspary 1988). Michler's ketone caused chromosomal aberrations in Chinese hamster ovary (CHO) cells (NTP 1990) and in Chinese hamster embryo CHE-3N cells (Lafi et al. 1986). Michler's ketone also induced sister chromatid exchange in CHO cells (NTP 1990) and caused cell transformation in Balb/c 3T3 cells (Tennant et al. 1986). In bacterial bioassays, Michler's ketone was mutagenic in *Salmonella typhimurium* TA98 in the presence of S9 (Dunkel et al. 1985; Tennant et al. 1986; Zeiger et al. 1992) and in TA1538, which detects frameshift mutations (Dunkel and Simmon 1980), whereas it was not mutagenic in strains TA97, TA100, TA1535 and TA1537, which detect base pair substitution (Scribner et al. 1980; McCarthy et al. 1983; Tennant et al. 1986) or in TA98 without S9 (Zeiger et al. 1992). All the lines of evidence from mutagenicity, cytogenicity and DNA damage support the conclusion that Michler's ketone is genotoxic to mammalian somatic cells *in vitro* and *in vivo*. This conclusion is supported by the European Commission's classification of Michler's ketone as a Mutagen Category 3 substance based on *in vivo* genotoxicity in somatic cells (European Commission 2002, 2004; ESIS 2009).

The detailed modes of action for hepatocellular carcinomas and hemangiosarcomas have not been proposed or developed by other regulatory agencies, and the development and analysis of modes of action are normally outside the scope of a screening-level risk assessment. Based on the weight of evidence of carcinogenicity observed in both sexes of both species in 2-year experimental animal studies, including hepatocellular carcinomas observed at the lowest test doses, and the evidence that Michler's ketone is genotoxic in a range of *in vivo* and *in vitro* assays, including binding and damage to liver DNA, it is reasonably concluded that the tumours observed in the experimental animals are likely to have resulted from direct interaction with genetic material.

With regard to repeated-dose short-term and chronic toxicity, the reported most sensitive non-cancer critical effect for characterization of risk to human health from Michler's ketone is reduced body weight gain. In a short-term study, the lowest oral lowest-observed-adverse-effect level (LOAEL) of 68 mg/kg-bw per day was determined based on significantly reduced body weight gain (less than 40% of the control) in F344 rats exposed to Michler's ketone in the diet at 0, 68, 147, 316, 680 or 1467 mg/kg-bw per day for 4 weeks followed by 2 weeks of observation. In addition, the survival rates decreased at higher doses (i.e., two deaths out of five animals at 316 mg/kg-bw per day) (National Cancer Institute 1979). In a chronic study, the lowest oral LOAEL of 12.5 mg/kg-bw per day was identified in male rats based on reduced body weight gain (National Cancer Institute 1979); however, at this LOAEL, significantly induced tumours were observed as well. In the dataset, no studies were conducted at exposure levels lower than 12.5 mg/kg-bw per day.

A limited toxicokinetic study showed that demethylation, N-hydroxylation and N-acetylation appeared to be the major transformation pathways for Michler's ketone in rats (Struck et al. 1981). The major metabolites identified in the bile (after intravenous injection) were the di- and tri-demethylated derivatives and the N-acetylated tetra-demethylated compound. It is proposed that following demethylation of Michler's ketone, the metabolites of aromatic amines could be subject to N-hydroxylation or N-acetylation to form active metabolites that could bind to macromolecules and be responsible for the carcinogenicity of Michler's ketone (Struck et al. 1981).

The confidence in the toxicity database for Michler's ketone is considered to be moderate in the screening assessment. Oral dosing studies (short-term, carcinogenicity and genotoxicity) are available; however, no reproductive toxicity or developmental toxicity studies are available. In addition, effects, including carcinogenicity, occurred at the lowest exposure levels tested. Most of the experimental animal studies were carried out through oral exposure (in diet), and experimental animal studies via inhalation or dermal exposure are not available. In addition, the modes of action for the observed carcinogenicity of Michler's ketone have not been elaborated.

### **Characterization of Risk to Human Health**

Based principally on the weight of evidence-based assessments of international or other national agencies (European Commission 2002, 2004; NTP 2005; Baan et al. 2008), a critical effect for the characterization of risk to human health from Michler's ketone is carcinogenicity. Incidences of hepatocellular carcinomas in male and female rats and female mice were increased in a dose-related manner, and increased incidences of hemangiosarcomas in male mice were observed. Significant levels of hepatocellular carcinomas were observed at the lowest doses tested. Michler's ketone was genotoxic in a range of *in vivo* and *in vitro* assays. Although the detailed modes of action for the increased incidence of hepatocellular carcinomas and hemangiosarcomas have not been developed, based on the weight of evidence of carcinogenicity and the genotoxicity of Michler's ketone, the tumours observed in the experimental animals are considered to have resulted from direct interaction with genetic material.

Among the non-cancer critical effects, the most sensitive endpoint is the reduced body weight gain, with an oral LOAEL of 12.5 mg/kg-bw per day identified in male rats in a chronic study (National Cancer Institute 1979). However, at this LOAEL, tumours were observed as well; therefore, a margin of exposure is not calculated for the non-cancer effects in the current screening assessment.

Exposures of the general population to Michler's ketone through environmental media (air, drinking water and soil) is expected to be negligible. For environmental media, the upper-bounding estimate of daily intake for all age groups of the general Canadian population was <0.01 µg/kg-bw per day.

Based upon the information obtained on current use of Michler's ketone in Canada, exposure of the general population is expected to be very low and limited to the use of

non-food-related paper products containing residual Michler's ketone in the paper colourants. Exposure of the general population to Michler's ketone from other consumer products such as ball pens is expected to be of less concern as most Michler's ketone in Canada is used for paper products. A scenario developed for the oral exposure of consumers to paper products was used for calculating maximum intakes. The upper bound intake by a child (aged 0.5–4 years) was  $8 \times 10^{-4}$  mg/kg-bw per event. A scenario developed for the oral and dermal exposure of consumers to ball pens was used for calculating maximum intakes. The upper bound intake by a child (aged 0.5–4 years) was  $4 \times 10^{-3}$  mg/kg-bw per event.

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

The scope of this screening assessment does not take into account possible differences between humans and experimental species in sensitivity to effects induced by this substance, particularly in light of the limited data available for humans and the absence of physiologically based pharmacokinetic models developed for Michler's ketone in either experimental animals or humans. It is assumed that the similar effects observed in both rodent species may be relevant to humans. Additionally, the modes of tumour induction have not been analysed or elucidated. There is limited toxicological information on non-cancer endpoints, including developmental and reproductive toxicity. The absence of a LOAEL for a non-cancer endpoint, which is lower than the levels with tumour induction, precludes calculating the margin of exposure for non-cancer effects. In addition, the experimental animal studies involve oral administration only, not inhalation or dermal exposure.

There is uncertainty regarding the estimation of population exposures because of the use of modelling and the lack of Canadian data. There is uncertainty associated with the assumptions incorporated into the consumer product scenario models, including the parameters used, specific types of products containing Michler's ketone and the quantity and frequency of use in Canada. Exposures of children 0.5–4 years of age to Michler's ketone from oral paper contact are considered overestimates, as the assumptions incorporated are conservative and the concentration of Michler's ketone in paper products used in this scenario may not be representative of paper typically used by children. There is uncertainty with regard to the ball pen scenario, as it was adapted from a scenario for felt markers. There is also uncertainty as ink-based ball pen and permanent marker use by children is expected to be limited. Limited information was available in the literature regarding the use of Michler's ketone in markers. There were limited consumer product scenarios available. There is uncertainty with regard to the potential presence of Michler's ketone residues in textiles in Canada. One section 71 reporter has confirmed that they do not use colourants for textiles (2009 personal communication from industry to Existing Substances Bureau, Health Canada; unreferenced). However, a literature search indicated that Michler's ketone has been found in textiles internationally. Data gaps for oral exposure are likely more critical than those for inhalation and dermal exposures, because it is the primary route of exposure. Environmental releases to media other than air are another uncertainty. It may also be possible for increased exposure to Michler's ketone to occur from the use of crystal violet where degradation of the dye has

occurred. However, the total amount of Michler's ketone imported and used in Canada suggests that exposure will likely be low.

## Conclusion

Based on the information presented in this final screening assessment, it is concluded that Michler's ketone 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, Michler's ketone meets the criteria for persistence as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000) but does not meet the criteria for bioaccumulation potential as specified in the Regulations.

On the basis of the carcinogenicity of Michler's ketone, for which there may be a probability of harm at any level of exposure, and the evidence that tumours are observed at the lowest tested doses, it is concluded that Michler's ketone is a substance that may be 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 Michler's ketone meets one or more of the criteria set out in section 64 of CEPA 1999.

Where relevant, research and monitoring will support verification of assumptions used during the screening assessment and, where appropriate, the performance of potential control measures identified during the risk management phase.

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### Appendix 1: Upper-bounding estimates of exposure to Michler's ketone from ingestion of paper by children aged 6 months to 4 years

Consumer product	Assumptions	Exposure estimate (mg/kg-bw per event)
Paper (multi-use)	<p>For standard multi-use paper, 500 sheets (dimensions 17 × 22 inches per sheet) weigh ~ 9 kg; therefore, one sheet weighs (9 kg)/500 = 0.018 kg.</p> <p>As a standard sheet of paper has dimensions of 8.5 × 11 inches, one standard sheet of paper weighs (0.018 kg) × [(8.5 × 11)/(17 × 22)] or ~0.0045 kg (~4.5 g).</p> <p>It was very conservatively assumed that ¼ of all of the Michler's ketone in a sheet of paper was ingested (~ 1 g of paper).</p> <p>The highest concentration of Michler's ketone detected in recycled paper/paperboard is 12.0 µg/g (1.2 × 10<sup>-2</sup> mg/g).<sup>1</sup></p> <p>It was assumed that the Michler's ketone was completely absorbed.</p> <p><b>Estimated oral intake:</b> Intake = [Concentration (w/w) of Michler's ketone in paper × weight of paper eaten] / body weight</p> <p>For children 0.5–4 years<sup>2</sup>: Intake = [(1.2 × 10<sup>-2</sup> mg/g) × (1 g)] / 15.5 kg = 8 × 10<sup>-4</sup> mg/kg-bw</p>	<p>Oral exposure, for children 0.5–4 years:</p> <p>8 × 10<sup>-4</sup> mg/kg-bw per event</p>

<sup>1</sup> The highest Michler's ketone concentration in paper was obtained from a literature search. From this reference, Michler's ketone was only found in recycled paper materials and not virgin paper products (Ozaki et al. 2004).

<sup>2</sup> Body weight assumed to be 15.5 kg (Health Canada 1998).



## Appendix 2: Upper-bounding estimate of dermal and oral exposure to Michler's ketone from ball pens and markers for children aged 6 months to 4 years

Consumer Product	Estimated daily dermal or oral exposure <sup>1</sup>	Exposure estimates (mg/kg-bw per event)
Ball pen and marker	<p><b>ACUTE / SHORT-TERM EXPOSURE:</b></p> <p>It is assumed that an area corresponding to two child palms of 5*5 cm (50 cm<sup>2</sup>) could be covered with ink (Danish EPA 2008). The amount of ink transferred to 50 cm<sup>2</sup> was estimated to be 50 mg for marker pens (Danish EPA 2008).</p> <p><b>Intake</b> = (Concentration of Substance in pen ink (w/w) x estimated amount of ink per exposure (50 mg) x fraction absorbed) / body weight (kg)</p> <p><b>Parameters used:</b> Maximum Michler's ketone concentration: 0.124%<sup>2</sup> (0.00124 w/w fraction); body weight of 15.5 kg for 0.5- to 4-year-old children (Health Canada 1998)<sup>3</sup></p> <p><b>Intake</b> = (0.00124 × 50 mg × 1) / 15.5 kg = 4 × 10<sup>-3</sup> mg/kg-bw</p> <p><b>CHRONIC EXPOSURE:</b></p> <p>The Art and Creative Materials Institute (ACMI), Duke University reported the assumption that a child will absorb 25 cm of ink line daily either through dermal or incidental oral exposure (2009 personal communication to Health Canada).<sup>1,4</sup> Michler's ketone was found in pens (concentration range of 0.0023-0.11%) with an ink laydown rate of 2-7 ug/cm and markers (concentration range of 0.00024-0.13%) with an ink laydown rate of 100-352 ug/cm<sup>5</sup></p> <p><b>For children 0.5 - 4 years:</b></p> <p><b>Intake</b> = [(Concentration of Michler's ketone in pen or marker ink (w/w) x ink laydown rate (ug/cm) x 25 cm ink line/day) / 1000] / 15.5 kg</p> <p><b>Pen Intake (low to high)</b> = 7.42 x 10<sup>-8</sup> to 1.24 x 10<sup>-5</sup> mg/kg-bw</p> <p><b>Marker Intake (low to high)</b> = 3.87 x 10<sup>-7</sup> to 7.38 x 10<sup>-4</sup> mg/kg-bw</p>	<p>Oral and dermal exposure, for children 0.5–4 years:</p> <p>Acute/short-term: 4 x 10<sup>-3</sup> mg/kg-bw per event</p> <p>Chronic: 7.42 x 10<sup>-8</sup> to 7.38 x 10<sup>-4</sup> mg/kg-bw per day</p>

<sup>1</sup> This scenario covers both dermal and incidental oral exposure from sucking the object or from hand-to-mouth exposure and is conservative in that it assumes daily exposure for the life time of the child or adult, therefore actual exposure will likely be lower. 100% absorption is assumed (to cover off hand-to-mouth and object exposure), however depending on the properties of the substance this will be an overestimate for dermal exposure and for oral exposure in adults (assumed to be negligible).

<sup>2</sup> Concentration of 0.124% obtained from the State Library of the Canton Basel City. This concentration is based on an HCl extract, with which ingestion via the stomach was simulated (Basel-Stadt 2003).

<sup>3</sup> This age range is considered to be the most highly exposed through the use of markers or pens, particularly in terms of mouthing (US EPA 2008)

<sup>4</sup> This assumption was reviewed and considered conservative by the US Consumer Product Safety Commission's Health Science Directorate and the California Department of Health Services (2009 personal communication to Health Canada from ACMI).

<sup>5</sup> (2009 personal communication to Health Canada from ACMI)

**Appendix 3. Summary of health effects information for Michler's ketone**

<b>Endpoint</b>	<b>Lowest effect levels<sup>1</sup>/Results</b>
<b>Experimental animals and cells</b>	
Acute toxicity	<b>Oral LD<sub>50</sub></b> (wild bird) = 100 mg/kg-bw (Schafer et al. 1983).
Short-term repeated-dose toxicity	<p><b>Lowest oral LOAEL:</b> 68 mg/kg-bw per day based on decreased body weight gain (-40%) in F344 male rats (5 per sex per group) exposed to Michler's ketone in the diet at a concentration of 0, 680, 1465, 3155, 6800 or 14 665 mg/kg (providing 0, 68, 147, 316, 680 or 1467 mg/kg-bw per day) for 4 weeks followed by 2 weeks of observation. Two out of five female rats died at 316 mg/kg-bw per day (National Cancer Institute 1979).</p> <p><b>Other oral LOAEL:</b> 600 mg/kg-bw per day based on reduced body weight gain in B6C3F1 mice (5 per sex per group) exposed to Michler's ketone in the diet at a concentration of 0, 440, 1390, 3000, 6400 or 13 900 mg/kg (providing 0, 88, 275, 600, 1280 or 2780 mg/kg-bw per day) for 4 weeks followed by 2 weeks of observation (National Cancer Institute 1979).</p> <p>No inhalation or dermal studies were identified.</p>
Chronic toxicity/carcinogenicity	<p><b>Oral carcinogenicity in rats:</b> A group of 50 male Fischer 344 rats (20 controls) was administered Michler's ketone in the diet at a concentration of 0, 250 or 500 mg/kg (corresponding to 0, 12.5 and 25 mg/kg-bw per day) for 78 weeks followed by an observation period of 28 weeks. Incidences of hepatocellular carcinoma were significantly increased in a dose-related manner (0/20, 9/50 and 40/50 for 0, 12.5 and 25 mg/kg-bw per day, respectively). Similarly, a group of 50 female Fischer 344 rats (20 controls) was administered Michler's ketone in the diet at a concentration of 0, 500 or 1000 mg/kg (corresponding to 0, 25 and 50 mg/kg-bw per day) for 78 weeks followed by an observation period of 28–29 weeks. Incidences of hepatocellular carcinoma were also significantly increased in a dose-related manner in female rats (0/20, 41/47 and 44/49 for 0, 25 and 50 mg/kg-bw per day, respectively). The combined incidence of neoplastic lesions (hepatocellular carcinoma and neoplastic nodules) increased significantly at both doses in both sexes (National Cancer Institute 1979).</p> <p><b>Oral carcinogenicity in mice:</b> Groups of 50 male and 50 female B6C3F1 mice were administered Michler's ketone in the diet at a concentration of 0, 1250 or 2500 mg/kg (corresponding to 0, 179 and 357 mg/kg-bw per day) for 78 weeks followed by an observation period of 13 weeks. In female mice, incidences of hepatocellular carcinoma increased significantly in a dose-related manner (0/19, 16/49 and 38/50 for 0, 179 and 357 mg/kg-bw per day, respectively). In male mice, no significantly increased incidences of hepatocellular carcinoma were observed, but a significantly increased incidence of hemangiosarcoma was observed in the circulatory system at the high dose (0/19, 5/50 and 20/50 for 0, 179 and 357 mg/kg-bw per day, respectively) (National Cancer Institute 1979).</p> <p><b>Non-neoplastic effects:</b> In the same studies described above for rats and mice in both sexes, a dose-related mean body weight depression was apparent throughout the bioassay. A dose-related survival rate was observed for rats, and a reduced survival rate was seen for male mice at the top dose. A LOAEL of 12.5 mg/kg-bw per day was identified in male rats and a LOAEL of 179 mg/kg-bw per day was identified in male mice based on reduced body weight gain (National Cancer Institute 1979). However, at these LOAELs, tumours were observed as well.</p> <p>No inhalation or dermal studies were identified.</p>
Genotoxicity and related endpoints: <i>in vitro</i> bacteria	<p><b>Mutagenicity</b></p> <p><b>Positive:</b> In <i>Salmonella typhimurium</i> TA98 in the presence of induced rat or hamster liver S9. The doses ranged from 0 to 10 mg/plate (Dunkel et al. 1985; Tennant et al.</p>

Endpoint	Lowest effect levels <sup>1</sup> /Results
	<p>1986; Zeiger et al. 1992). A positive result was also observed in TA1538 (Dunkel and Simmon 1980).</p> <p><b>Negative:</b> In <i>Salmonella typhimurium</i> TA97, TA100, TA1535 and TA1537 in the presence or absence of metabolic activation by induced rat and hamster liver S9 (Tennant et al. 1986). Negative results were also observed in TA98 without induced liver S9 (Zeiger et al. 1992), TA1538 and TA100 (Scribner et al. 1980; McCarthy et al. 1983).</p> <p><b>Negative:</b> In <i>Escherichia coli</i> strain WP2 uvrA at concentrations up to 3.3 mg/plate with or without rat mouse or hamster liver S9 metabolic activation (Dunkel et al. 1985).</p> <p><b>DNA damage</b>  <b>Negative:</b> No growth inhibition observed in <i>Rec</i> assay in <i>Bacillus subtilis</i> strains M45 <i>Rec</i><sup>-</sup> and H17 <i>Rec</i><sup>+</sup> up to 1 mg/disc (Ozaki et al. 2004).</p> <p><b>Negative:</b> In SOS chromotest in <i>Escherichia coli</i> strain PQ37 with or without S9 metabolic activation (von der Hude et al. 1988).</p>
Genotoxicity and related endpoints: <i>in vitro</i> mammalian cells	<p><b>Mutagenicity</b>  <b>Positive:</b> A dose-dependent increase in mutation frequencies seen in mouse lymphoma L5178Y cells in the presence or absence of metabolic activation by induced liver S9 (Mitchell et al. 1988; Myhr and Caspary 1988).</p> <p><b>Chromosomal aberration</b>  <b>Positive:</b> In Chinese hamster ovary (CHO) cells exposed to 65–300 µg Michler’s ketone/ml in the presence of S9 with harvest time 16.5–20.5 h (NTP 1990).  <b>Positive:</b> In Chinese hamster embryo CHE-3N cells exposed to up to 1.5 µg Michler’s ketone/ml (Lafi et al. 1986).  <b>Negative:</b> In CHO cells exposed to 65–300 µg Michler’s ketone/ml in the absence of S9 (NTP 1990) or up to 5 mg Michler’s ketone/ml in the presence or absence of S9 with harvest time 12–14 h (NTP 1983).</p> <p><b>Sister chromatid exchange</b>  <b>Positive:</b> In CHO cells exposed to up to 300 µg Michler’s ketone/ml in the presence or absence of S9 (NTP 1990).</p> <p><b>Aneuploidy</b>  <b>Positive:</b> In Chinese hamster embryo CHE-3N cells exposed to Michler’s ketone at a concentration of 0.75 or 1.5 µg/ml (Lafi et al. 1986).</p> <p><b>Cell transformation assay</b>  <b>Positive:</b> In Balb/c 3T3 cells without S9 (Tennant et al. 1986).  <b>Positive:</b> In RLV-infected rat embryo (RE) cells (Heidelberger et al. 1983).</p> <p><b>DNA damage</b>  <b>Negative:</b> No DNA damage (by comet assay) observed in HL-60 cells (human promyelocytic leukemia cell) exposed to Michler’s ketone at concentrations up to 25 µg/ml (Ozaki et al. 2004).</p>
Genotoxicity and related endpoints: <i>in vivo</i>	<p><b>Sister chromatid exchange</b>  <b>Positive:</b> Michler’s ketone induced sister chromatid exchange in bone marrow in Swiss mice administered by intraperitoneal injection at a dose of 7.5, 15 or 30 mg/kg-bw (Parodi et al. 1982)</p> <p><b>DNA binding</b></p>

Endpoint	Lowest effect levels <sup>1</sup> /Results
	<p><b>Positive:</b> Michler's ketone bound to liver DNA in male Fischer 344 rats administered radiolabelled materials at a dose of 0.009, 0.9 or 9 mg/rat by intraperitoneal injection (Scribner et al. 1980).</p> <p><b>Positive:</b> Bound to the DNA of liver and kidney of phenobarbital-pretreated Osborne-Mendel rats administered <sup>14</sup>C-labelled Michler's ketone at a dose of 2.5 mg/rat by intraperitoneal injection (Struck et al. 1981).</p> <p><b>DNA damage</b></p> <p><b>Positive:</b> Michler's ketone induced unscheduled DNA synthesis in male Fischer 344 rats exposed to Michler's ketone at a dose of 200 or 1000 mg/kg-bw by gavage (Mirsalis et al. 1989).</p> <p><b>Positive:</b> Michler's ketone caused liver DNA damage assessed by alkaline elution assay in Sprague-Dawley rats at 7.5 or 15 mg/kg-bw administered by intraperitoneal injection (Parodi et al. 1982).</p> <p><b>Positive:</b> Michler's ketone caused liver DNA damage assessed by alkaline elution assay in Sprague-Dawley CD rats at 150 mg/kg bw administered by gavage (Kitchin and Brown 1994).</p>
<b>Humans</b>	No epidemiological data were available.

<sup>1</sup> LD<sub>50</sub>, median lethal dose; LOAEL, lowest-observed-adverse-effect level.