Government of Canada / Gouvernement du Canada

PROPOSED RISK MANAGEMENT APPROACH

for

Methanone, bis[4-(dimethylamino)phenyl]-

(Michler's ketone)

Chemical Abstracts Service Registry Number (CAS RN):
90-94-8

Environment Canada
Health Canada

March 2010

Canada

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This proposed risk management approach document builds on the previously released risk management scope document for Michler's ketone, and outlines the proposed control actions for this substance. Stakeholders are invited to submit comments on the content of this proposed risk management approach or provide other information that would help to inform decision making. Following this consultation period, the Government of Canada will initiate the development of the specific risk management instrument(s) where necessary. Comments received on the proposed risk management approach will be taken into consideration in developing the instrument(s). Consultation will also take place as instrument(s) are developed.

SUMMARY OF RISK MANAGEMENT

1. Michler's ketone will be added to the Health Canada Cosmetic Ingredient Hotlist.
2. The Government of Canada will require notification regarding any potential changes in the use pattern of Michler's ketone.

Note: This summary is an abridged list of the instruments and tools proposed to risk manage this substance. Please see section 9.1 of this document for a complete explanation of the proposed risk management.

1. ISSUE

1.1 Categorization and the Challenge to Industry and Other Interested Stakeholders

The *Canadian Environmental Protection Act, 1999* (CEPA 1999) (Canada 1999) requires the Minister of the Environment and the Minister of Health (the Ministers) to categorize substances on the *Domestic Substances List* (DSL). Categorization involves identifying those substances on the DSL that, in accordance with the criteria at section 73 of the Act, a) are considered to be persistent (P) and bioaccumulative (B), based on the criteria set out in the *Persistence and Bioaccumulation Regulations,* and "inherently toxic" (iT) to humans or other organisms; or b) may present, to individuals in Canada, the greatest potential for exposure (GPE). In addition, the Act requires the Ministers to conduct screening assessments of substances that meet the categorization criteria. The assessment further determines whether the substance meets one or more of the criteria of section 64 of the Act[1].

In December 2006, the Challenge identified 193 chemical substances through categorization which became high priorities for assessment due to their hazardous properties and their potential

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

to pose risks to human health and the environment. In February 2007, the Ministers began publishing, for industry and stakeholder comments, profiles of batches containing 12 to 19 high-priority substances. New batches are released for comments every three months.

Information-gathering authority in section 71 of CEPA 1999 is being used under the Challenge to gather specific information where it is required. The information that is collected through the Challenge is used to make informed decisions and appropriately manage any risks that may be associated with these substances.

The substance Methanone, bis[4-(dimethylamino)phenyl]-, Chemical Abstracts Service Registry Number (CAS RN)[2] 90-94-8, referred to throughout this document as "Michler's ketone," is included in Batch 7 of the Challenge under the Chemicals Management Plan.

1.2 Final Screening Assessment Report Conclusion for Michler's Ketone

A notice summarizing the scientific considerations of a final screening assessment report was published by Environment Canada and Health Canada in the *Canada Gazette*, Part I, for Michler's ketone on March 6, 2010, under subsection 77(6) of CEPA 1999. The final screening assessment report concluded that Michler's ketone is entering or may be entering the environment in a quantity or a concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

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 proposed 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 proposed that Michler's ketone does not meet the criteria in paragraphs 64(*a*) and 64(*b*) of CEPA 1999, but it does meet the criteria in paragraph 64(*c*) of CEPA 1999.

The final screening assessment report also concluded that Michler's ketone meets the criteria for persistence and does not meet the criteria for bioaccumulation, as defined in the *Persistence and Bioaccumulation Regulations* made under CEPA 1999. The presence of Michler's ketone in the environment results primarily from human activity.

For further information on the final screening assessment report conclusion for Michler's ketone, refer to the final screening assessment report, available at http://www.chemicalsubstanceschimiques.gc.ca/challenge-defi/batch-lot-7/index-eng.php.

[2] CAS RN: Chemical Abstracts Service Registry Number. The Chemical Abstracts Service information is the property of the American Chemical Society, and any use or redistribution, except as required in supporting regulatory requirements and/or for reports to the Government of Canada when the information and the reports are required by law or administrative policy, is not permitted without the prior written permission of the American Chemical Society.

1.3 Proposed Measure

As a result of a screening assessment of a substance under section 74 of CEPA 1999, the substance may be found to meet one or more of the criteria under section 64 of CEPA 1999. The Ministers can propose to take no further action with respect to the substance, add the substance to the Priority Substances List (PSL) for further assessment, or recommend the addition of the substance Schedule 1 of the Act. Under certain circumstances, the Ministers must make a specific proposal to recommend the implementation of virtual elimination. In this case, the Minister proposed to recommend the addition of Michler's ketone to Schedule 1. As a result, the Ministers will develop a regulation or instrument respecting preventive or control actions to protect the health of Canadians and the environment from the potential effects of exposure to this substance.

Michler's ketone is not subject to the virtual elimination provisions under CEPA 1999 and will be managed using a life-cycle approach.

2. BACKGROUND

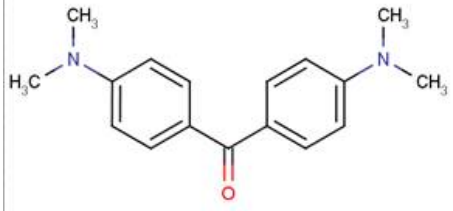
2.1 Substance Information

Michler's ketone is part of the chemical grouping discrete organics and the chemical sub-grouping ketones.

Table 1 presents other names, trade names, chemical groupings, the chemical formula, the chemical structure and the molecular mass for Michler's ketone.

Table 1. Identity of Michler's ketone

CAS RN	**90-94-8**
DSL name	**Methanone, bis[4-(dimethylamino)phenyl]-**
NCI names	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)
Other names	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
Chemical group (DSL stream)	Discrete organics

Major chemical class or use	Ketones
Major chemical subclass	Benzophenones
Chemical formula	$C_{17}H_{20}N_2O$
Chemical structure	
SMILES	O=C(c(ccc(N(C)C)c1)c1)c(ccc(N(C)C)c2)c2
Molecular mass	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

3. WHY WE NEED ACTION

3.1 Characterization of Risk

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 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, it is reasonably concluded that the tumours observed in the experimental animals are likely to have resulted from direct interaction with genetic material.

Among the non-cancer critical effects, the most sensitive endpoint is reduced body weight gain, with an oral lowest-observed-adverse-effect level (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.

4. CURRENT USES AND INDUSTRIAL SECTORS

Michler's ketone was not manufactured in Canada in 2006 at quantities greater than or equal to 100 kg. Imports were between 100 and 1000 kg, while uses were between 1000 and 10 000 kg.

Michler's ketone is a water-insoluble, blue powder or white-to-green-coloured leaf-like material upon purification. Michler's ketone results from an intermediate reaction during the manufacturing of dye colorants and pigments and consequently is found in certain dye colorants and pigments as a residual (Environment Canada 2008). The most probable exposure of the general population in Canada is from exposures to such residuals in certain dye colorants and pigments used in paper products, with lesser contributions from other pigment-containing products. Some examples of paper colorants that may contain residual Michler's ketone include Crystal Violet, Basazol Violet, Basic Brown C2, Basic Purple 48 and Methyl Violet. Michler's ketone is also a major degradation product of the dye Crystal Violet. It can also be demethylated to [N,N-dimethylaminophenyl] [N-methylaminophenyl] benzophenone. According to submissions made under section 71 of CEPA 1999 and from the Challenge questionnaire submissions (Environment Canada 2008), the majority of Michler's ketone used in Canada may be found as a residue in paper colorant (colorant – dye, pigment, stain, ink) at a concentration of 0.009–4.5 w/w% (primarily $\leq$ 1%). It is present as a residual in dyes and pigments resulting from an intermediary reaction during manufacturing. It could potentially be present in industries involved in manufacturing paper or converting manufactured paper into different forms. It could be present in paper mills or newsprint mills (Environment Canada 2008). Michler's ketone can be found as a residue in some paper products and raw materials. Some of these products may be available to the public (Environment Canada 2008). Minor Canadian uses of Michler's ketone include its industrial use in dry films and in electronics manufacturing.

From a literature search, it was found that Michler's ketone is a chemical intermediate used in the synthesis of a variety of dyes and pigments, particularly auramine derivatives (NTP 2005). Auramine dyes can be used to dye paper, textiles and leather and can be used as an antiseptic fungicide or to colour ballpoint pen pastes and inks (NTP 2005; Thetford 2000; HSDB 1983; Cheminfo 2008; National Cancer Institute 1979; Merck Index 2006; Gessner and Mayer 2000). A current material safety data sheet (MSDS) indicated that less than 1% of Michler's ketone is present in the final pen product and at amounts up to approximately 0.1% in various pen inks tested (Basel-Stadt 2003). In Canada, the principal reported presence of Michler's ketone was as a residual in paper colorants. 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.

Outside Canada, Michler's ketone has been reported for use as a UV initiator for UV curing, e.g., in UV-cured printing inks for carton-board by 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., DEAB/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; Salafranca and Franz 2000; Nagarajan et al. 2000). In Canada, Michler's ketone has been reported as a trace impurity in inks for food packaging

applications (2009 personal communication from Food Directorate, Health Canada, to Existing Substances Bureau, Health Canada; unreferenced).

In Canada, since Michler's ketone is not listed in the Drug Product Database, the Natural Health Products Ingredients Database or the Licensed Natural Health Products Database, it is not expected to be present in pharmaceutical and natural health products as a medicinal or non-medicinal ingredient. 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, since it is known that uses outside Canada can include its use as a chemical intermediate in the manufacture of pharmaceuticals.

5. PRESENCE IN THE CANADIAN ENVIRONMENT AND EXPOSURE SOURCES

5.1 Releases to the Environment

Based on information collected through a survey conducted pursuant to section 71 of CEPA 1999, one facility involved in colorant 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. Some other facilities use a sewage treatment system to minimize releases and limit environmental exposure (Environment Canada 2008).

Michler's ketone (and its salts) are reportable to the National Pollutant Release Inventory (NPRI 2008). There were no releases reported under the NPRI.

5.2 Exposure Sources

The primary routes of exposure to Michler's ketone in Canada were concluded to be from oral or dermal contact with residues of Michler's ketone found in paper products.

No environmental media monitoring studies were reported for Michler's ketone levels in air, water, soil or sediment. Exposures of the general population to Michler's ketone through environmental media were not expected. In Canada, Michler's ketone can be found as a residual in trace amounts in some colour concentrates intended for paperboard. As such applications are only intended for dry food, there would be no expected migration of Michler's ketone into food. It is possible that low levels of Michler's ketone could be found in recycled paper products; however, because food packaged in recycled paperboard products is used with a protective coating and/or for foods that are already prepackaged (i.e., a functional barrier would be present), there would be no direct contact with food. Consequently, there would be no exposure to Michler's ketone from food.
Based upon the information obtained on current uses of Michler's ketone in Canada, potential exposure to the general population would be limited to oral and dermal exposures to paper products containing Michler's ketone as a manufacturing residual in paper colorants. However,

the exposure estimates are considered to be overestimates, as the assumptions incorporated are conservative. Exposure of the general population to Michler's ketone from other consumer products is expected to be low, as the majority of Michler's ketone used in Canada is for such paper products.

6. OVERVIEW OF EXISTING ACTIONS

6.1 Existing Canadian Risk Management

The safety of all material used for packaging foods is controlled under Division 23 of the *Food and Drug Regulations*, section B.23.001, which essentially prohibits the sale of a food in a package that may impart a harmful substance to its contents.

Michler's ketone (and its salts) are subject to reporting under the National Pollutant Release Inventory (NPRI) if thresholds for reporting are met.

6.2 Existing International Risk Management

United States

Michler's ketone is on the Hazardous Substance List for the New Jersey Department of Health. It is a listed carcinogen on the Special Health Hazard Substance List.

The U.S. Environmental Protection Agency (U.S. EPA), under the *Emergency Planning and Community Right-To-Know Act*, lists Michler's ketone as a Toxics Release Inventory (TRI) chemical that is subject to reporting requirements.

The United States *Clean Air Act*, sec. 112 (40 CFR 61, Hazardous Air Pollutants), applies to products containing Michler's ketone.

Michler's ketone is listed on California's Proposition 65 as a known carcinogen and reproductive toxicant and thus requires warning. It is also listed on California's Air Toxics "Hot Spots" Chemicals List under *Assembly Bill 2588*.

Europe

According to Schedule 4 of the Cosmetic Products Group Standard 2006, Michler's ketone is listed as a component that cosmetic products must not contain.

The main regulatory framework for cosmetic products in the European Union market is the Council Directive 76/768 of 27 July 1976 on the approximation of the laws of the Member States relating to cosmetic products. Michler's ketone is on Annex II M3(B), the list of substances which must not form part of the composition of cosmetic products, of this Council Directive (76/768/EEC) (OJ L 262, 27.9.1976), p. 169.

7. CONSIDERATIONS

7.1 Alternative Chemicals or Substitutes

No information on potential substitutes for Michler's ketone was brought forward in the voluntary Challenge Questionnaire submissions or during the public comment period on the Risk Management Scope document.

7.2 Alternative Technologies and/or Techniques

No alternative technologies and/or techniques were identified that would minimize or eliminate the use and/or release of the substance.

7.3 Socio-economic Considerations

Socio-economic factors will be considered in the development of regulations, instrument(s) and/or tool(s) as identified in the *Cabinet Directive on Streamlining Regulation* (Treasury Board of Canada Secretariat 2007) and the guidance provided in the Treasury Board document *Assessing, Selecting, and Implementing Instruments for Government Action*.

7.4 Children's Exposure

A conservative consumer product scenario to estimate oral exposure to residual Michler's ketone in paper colorants from possible ingestion of paper by children was conducted. For children aged 6 months to 4 years, oral exposure per event was estimated to be 8×10^{-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 modelled 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 colorant in the paper.

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 (Hansen et al. 2008). The estimated conservative per-event dermal or oral exposure to ink from the pens was 4×10^{-3} mg/kg-bw in children aged 6 months to 4 years. 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.

The presence of Michler's ketone in pen inks was confirmed in Canada through laboratory testing. To date, Michler's ketone has not been identified in any children's markers. Preliminary results indicate that Michler's ketone is generally not present in the various paper products tested.

8. PROPOSED OBJECTIVES

8.1 Environmental or Human Health Objective

An environmental or human health objective is a quantitative or qualitative statement of what should be achieved to address environmental or human health concerns identified during a risk assessment.

The proposed human health objective for Michler's ketone is to minimize human exposure to the greatest extent practicable.

8.2 Risk Management Objective

A risk management objective is a target expected to be achieved for a given substance by the implementation of risk management regulations, instrument(s) and/or tool(s).

As current exposures to Michler's ketone were considered to be low under current use conditions, the risk management objective for Michler's ketone is to prevent increases in exposure.

9. PROPOSED RISK MANAGEMENT

9.1 Proposed Risk Management Tools

As required by the Government of Canada's *Cabinet Directive on Streamlining Regulation*[3] and criteria identified in the Treasury Board document entitled *Assessing, Selecting, and Implementing Instruments for Government Action*, the two proposed risk management tools were selected using a consistent approach, and took into consideration the information that was received through the Challenge and other information available at the time.

In order to achieve the risk management objective and to work towards achieving the environmental or human health objective(s), the following risk management is being considered for Michler's ketone**:**

[3] Section 4.4 of the *Cabinet Directive on Streamlining Regulation* states that "Departments and agencies are to: identify the appropriate instrument or mix of instruments, including regulatory and non-regulatory measures, and justify their application before submitting a regulatory proposal".

(1) **Require notification of the federal government regarding any potential changes in the use-pattern for Michler's ketone** so that the potential for exposure to the Canadian population does not increase
(2) As a preventative measure **the federal government will add Michler's ketone to the Health Canada Cosmetic Ingredient Hotlist as a prohibited substance**. The Cosmetic Ingredient Hotlist is an administrative tool to help manufacturers satisfy the cosmetic safety provisions of section 16 of the *Food and Drugs Act*. Compliance with the provisions of section 16 are monitored, in part, through the mandatory notification provisions of section 30 of the *Cosmetic Regulations* of the *Food and Drugs Act*, which requires that all manufacturers and importers provide a list of the cosmetic's ingredients to Health Canada.

9.2 Implementation Plan

The proposed regulation or instrument respecting preventative or control actions in relation to Michler's ketone will be published in the *Canada Gazette*, Part I, no later than March 2012, as per the timelines legislated in CEPA 1999.

10. CONSULTATION APPROACH

The risk management scope document for Michler's ketone, which summarized the proposed risk management under consideration at that time, was published on September 5, 2009. Industry and other interested stakeholders were invited to submit comments on the risk management scope document during a 60-day comment period. Comments received on the risk management scope document were taken into consideration in the development of this proposed risk management approach document.

Consultation for the proposed risk management approach document will involve publication on March 6, 2010, and a 60-day public comment period.

The primary stakeholders include

- dye and pigment manufacturers
- pulp and paper manufacturers
- non-governmental organizations

11. NEXT STEPS / PROPOSED TIMELINE

Actions	Date
Electronic consultation on proposed risk management approach document	March 6, 2010, to May 5, 2010
Response to comments on the proposed risk management approach document	No later than the time of publication of the

	proposed instrument
Consultation on the draft instrument	Fall-winter 2010–2011
Publication of the proposed instrument	No later than March 2012
Formal public comment period on the proposed instrument	No later than spring 2012
Publication of the final instrument	No later than September 2013

Industry and other interested stakeholders are invited to submit comments on the content of this proposed risk management approach or provide other information that would help to inform decision making. Please submit comments prior to May 5, 2010, since the risk management of Michler's ketone will be moving forward after this date. During the development of regulations, instrument(s) and tool(s), there will be opportunity for consultation. Comments and information submissions on the proposed risk management approach should be submitted to the address provided below:

Chemicals Management Division
Gatineau Quebec K1A 0H3
Tel: 1-888-228-0530 / 819-956-9313
Fax: 819-953-7155
Email: Existing.Substances.Existantes@ec.gc.ca

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