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Rotterdam Convention on the Prior Informed Consent Procedure for Certain Hazardous Chemicals and Pesticides in International Trade
Chemical Review Committee
First meeting
Geneva, 11–18 February 2005
Item 7 (j) of the provisional agenda*

Inclusion of chemicals in Annex III of the Rotterdam Convention: review of notifications of final regulatory actions to ban or severely restrict a chemical: benzidine

Benzidine

Note by the secretariat

1. In line with article 5 of the Rotterdam Convention on the Prior Informed Consent Procedure for Certain Hazardous Chemicals and Pesticides in International Trade, when the secretariat has received at least one notification from each of two prior informed consent (PIC) regions that contain the information required in Annex I to the Convention, it shall forward the notifications and accompanying documentation to the members of the Chemical Review Committee. The Committee shall review the information provided in such notifications and, in accordance with the criteria set out in Annex II, recommend to the Conference of the Parties whether the chemical in question should be included in Annex III and a decision guidance document drafted.

2. In addition to the four notifications from three PIC regions relating to benzidine (Europe – Latvia; Near East – Jordan; and Asia – India and Republic of Korea) considered in UNEP/FAO/RC/CRC.1/23, two additional notifications have now been verified by the secretariat, from Canada and Japan. Summaries of these notifications will be included in PIC Circular XXI, for June 2005. The notifications as they were received from the notifying countries are annexed to the present note.

3. The supporting documentation provided Canada and Japan, where available, will be found in documents UNEP/FAO/RC/CRC.1/23.Add.6 and Add.7, respectively.

* UNEP/FAO/RC/CRC.1/1.

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Annex

Interim Secretariat for the Rotterdam Convention on the Prior Informed Consent Procedure for Certain Hazardous Chemicals and Pesticides in International Trade

UNEP

FORM FOR NOTIFICATION OF FINAL REGULATORY ACTION TO BAN OR SEVERELY RESTRICT A CHEMICAL

IMPORTANT: See instructions before filling in the form

COUNTRY: CANADA

PART I: PROPERTIES, IDENTIFICATION AND USES

1.	**IDENTITY OF CHEMICAL**	
1.1	**Common name**	Benzidine Benzidine dihydrochloride (benzidine salt) Note: Benzidine salt is addressed with benzidine in this notification as it dissociates in water into benzidine.
1.2	**Chemical name according to an internationally recognized nomenclature (e.g. IUPAC), where such nomenclature exists**	Benzidine IUPAC: 4,4'-diaminobiphenyl Benzidine dihydrochloride IUPAC: [1,1-Biphenyl]-4,4'-diamine dihydrochloride
1.3	**Trade names and names of preparations**	Benzidine 1,1-'Biphenyl-4,4'-Diamine; 4,4'-diamino-1,1'-biphenyl; 4,4'-bianiline; 4,4'-biphenyldiamine; 4,4'-diaminobiphenyl; 4,4'-diphenylenediamine; p-benzidine; p-Diaminodiphenyl; Bensidine; benzidine base; C.I. 37225; C.I. azoic diazo component 112; fast corinth base b
1.4	**Code numbers**	
1.4.1	**CAS number**	Benzidine: 92-87-5 Benzidine dihydrochloride: 531-85-1
1.4.2	**Harmonized System customs code**	No information available
1.4.3	**Other numbers (specify the numbering system)**	Benzidine RTECS: DC9625000 EC: 612-042-00-2 UN: 1885 (Poison B) Benzidine dihydrochloride RTECS : DD0600000 UN: 1885 (Poison B)

PLEASE RETURN THE COMPLETED FORM TO:

Interim Secretariat for the Rotterdam Convention
Plant Protection Service
Plant Production and Protection Division, FAO
Viale delle Terme di Caracalla
00100 Rome, Italy

Tel: (+39 06) 5705 3441
Fax: (+39 06) 5705 6347
E-mail: pic@fao.org

OR

Interim Secretariat for the Rotterdam Convention
UNEP Chemicals

11-13, Chemin des Anémones
CH – 1219 Châtelaine, Geneva, Switzerland

Tel: (+41 22) 917 8183
Fax: (+41 22) 797 3460
E-mail: pic@unep.ch

1.5	Indication regarding previous notification on this chemical, if any
1.5.1	☑ This is a first time notification of final regulatory action on this chemical.
1.5.2	☐ This is a modification of a previous notification of final regulatory action on this chemical. The sections modified are: _____ ☐ This notification replaces all previously submitted notifications on this chemical.
	Date of issue of the previous notification: _____

1.6 Information on hazard classification where the chemical is subject to classification requirements	
International classification systems	**Hazard class**
No information available	m
Other classification systems	**Hazard class**
Benzidine: U.S. National Fire Protection Association (NFPA)	Health: 2, Flammability: 0, Reactivity: 0
Benzidine dihydrochloride: U.S. National Fire Protection Association (NFPA)	Health: 0, Flammability: 0, Reactivity: 0

1.7	Use or uses of the chemical
1.7.1	☐ **Pesticide**
	Describe the uses of the chemical as a pesticide in your country:
1.7.2	☑ **Industrial**
	Describe the industrial uses of the chemical in your country: Benzidine has been used primarily as an intermediate in the manufacture of dyes and pigments. It is not produced in Canada, and although it may have been imported in small amounts between 1980 and 1987, there no longer appears to be any commercial activity in Canada involving this substance. Benzidine and its salt are currently used only in very limited specialty laboratory applications, and for research and development purposes.

1.8 Properties

1.8.1 Description of physico-chemical properties of the chemical

Benzidine is a primary aromatic amine with the molecular formula $C_{12}H_{12}N_2$. At room temperature, benzidine is white or slightly red, and in the form of either crystals, powder or leaflets. Benzidine has:

- vapour pressure of 6.6×10^{-2} Pa at 25 °C [1]
- water solubility of 500 mg/L at 25 °C [1]
- log n-octanol/water partition coefficient of 1.34 [1]
- relative density of 1.25 (ratio of mass of benzidine to the mass of an equal volume of distilled water at 4 °C) [2]
- molecular weight of 184.2402 [2]
- melting point of 128 °C [2]
- boiling point of 401.7 °C [2]
- relative vapour density of 6.36 (ratio of the mass of benzidine to the mass of an equal volume of air, both at standard temperature and pressure) [2]
- Henry's Law Constant of 2.2×10^{-2} Pa m^3/mol [1]

Benzidine dihydrochloride is a white crystalline powder with the molecular formula $C_{12}H_{14}Cl_2N_2$. Benzidine dihydrochloride has:

- water solubility of 0.1-0.5 g/100 mL at 23.5°C [2]
- melting point > 300 °C [2]
- molecular weight of 257.162 [2]

[1] *Canadian Environmental Protection Act* Priority Substances List Assessment Report: Benzidine
[2] ChemFinder.com Database and Internet Searching (www.chemfinder.com)

1.8.2 Description of toxicological properties of the chemical

Experimental Animals and In Vitro

Based on data derived from studies involving predominantly experimental animals, it is apparent that benzidine may be metabolized via a number of metabolic routes. One metabolic pathway involves the acetylation of benzidine by cytosolic (acetyl-coenzyme A-dependent) N-acetyltransferase enzymes, which are present in many tissues. Humans (as well as some animal species) may be classified as either "fast" or "slow" acetylators, based on the extent to which they are able to acetylate a variety of chemical substances. Based on results of studies on individuals with and without bladder tumours, it has been proposed that this "acetylation polymorphism" may be associated with the development of bladder cancer in individuals exposed to aromatic amines—individuals with a "slow acetylator phenotype" may be more predisposed to develop bladder cancer than individuals with a "fast acetylator phenotype". Humans are capable of metabolizing benzidine-based azo dyes to benzidine.

The carcinogenicity of benzidine has been assessed in a number of animal species. An increased incidence of hepatocellular tumours (carcinomas, adenomas) has been observed in mice exposed to benzidine (in drinking water or in the diet) compared to unexposed controls. Rats administered benzidine (by gastric intubation of the substance dissolved in sesame oil) had a greater incidence of mammary lesions (i.e., carcinomas, adenomas, fibromas and hyperplasia) compared to controls administered vehicle alone. The incidence of liver tumours ("hepatomas and cholangiomas") was increased in Syrian hamsters administered benzidine (in the diet), compared to unexposed controls. A limited study reported the development of bladder carcinomas in 3 of 7 dogs administered (orally) benzidine for a period of 5 years. Benzidine is carcinogenic following injection (intraperitoneally; subcutaneously) in rodents (i.e., rats, mice), although such routes of exposure are considered less relevant to the assessment of risk than those by which humans are generally exposed (i.e., oral; inhalation). Results of a limited study in mice indicate that benzidine may induce tumours transplacentally.

Continued...

Though benzidine was not mutagenic nor did it bind covalently to DNA in some mammalian cells *in vitro*, the weight of evidence convincingly indicates that benzidine is mutagenic and genotoxic. It is mutagenic in prokaryotic and eukaryotic cells, has transformed a variety of rodent cells in *in vitro* assays, and increased sister chromatid exchange, unscheduled DNA synthesis and induced chromosomal aberrations in eukaryotic cells in *in vivo* and *in vitro* assays. Benzidine induced DNA damage in eukaryotic cells following *in vitro* or *in vivo* exposure, and the covalent binding of benzidine (i.e., its metabolites) to DNA has been observed following the *in vivo* exposure of experimental animals to this substance.

Mice administered drinking water containing benzidine dihydrochloride (20 to 160 mg/L) for their entire lifespan had vacuolation in the brain. Mice administered (by gavage) benzidine hydrochloride (10.8 to 43.2 mg/kg bw/day) for 5 consecutive days had diminished immunological function (i.e., reduced B- and T-cell mitogenic responses, reduced natural killer cell activity, delayed hypersensitivity responses and reduced resistance to infection). Data on the reproductive and developmental effects of benzidine on experimental animals were limited, and of little significance in assessing the toxicological effects of this substance.

Humans

In case reports and series published since 1927, the occurrence of bladder cancer in workers in Germany, Switzerland, Italy, England, Japan, France and the United States who had been occupationally exposed to benzidine has been reported.

It was reported that a significant ($p < 0.01$) standardized incidence ratio (SIR = 19.2) for bladder cancer (14 observed cases) in a group of males (n = 550) employed for at least 6 months between 1946 and 1976 in 7 factories in Shanghai producing benzidine-based dyes. The "standardized rate" for bladder cancer increased with increasing duration of exposure to benzidine. The average periods of exposure to benzidine and latency were 8 and 20 years, respectively.

A significant ($p < 0.01$) SIR (3.4, 95% confidence limit (CL) = 1.5 to 6.8) for cancer of the urinary bladder (8 observed cases/2.3 expected cases) was reported for a group of males (n = 830) employed for at least 1 day between 1945 and 1965 at a chemical plant in Connecticut producing benzidine and substituted benzidine compounds. SIRs for bladder cancer of 1.8 (95% CL = 0.05 to 10.1; 1 observed/0.55 expected), 0 (95% CL = 0 to 4.7; 0 observed/0.79 expected), 1.9 (95% CL = 0.05 to 10.7; 1 observed/0.52 expected) and 13 (95% CL = 4.8 to 28.4; 6 observed/0.46 expected) were reported for males in the unexposed, low-, medium- and high-exposure groups, (classified based on the duration of exposure to benzidine), respectively; however, a similar trend was not observed for "non-bladder" tumours. SIRs for bladder cancer of 0 (95% CL = 0 to 3.2; 0 observed/1.15 expected), 3.4 (95% CL = 0.4 to 12.4; 2 observed/0.58 expected) and 10 (95% CL = 3.6 to 21.7; 6 observed/0.6 expected) were reported for males employed at the plant from 0 to 1, 1 to 5 and more than 5 years, respectively. The SIR for bladder cancer (4 observed cases) for males occupationally exposed to benzidine between 1945 and 1949, was 9.8 (95% CL = 2.7 to 25), while the SIR based on 1 observed case was 2.1 for workers employed between 1950 and 1954 (95% CL = 0.05 to 11.9). Measures to reduce the exposure of workers to benzidine were introduced in 1950. The average latency period was approximately 20.9 years.

A significant ($p < 0.01$) standardized mortality ratio (SMR = 14.7) for deaths due to bladder cancer (5 observed cases) was reported in a group of males (n = 550) employed for at least 6 months between 1946 and 1976 in 7 factories in Shanghai producing benzidine-based dyes. It was also reported that a significant ($p < 0.01$) SMR (14.3) for deaths due to cancer of the "urinary organ" (3 observed deaths) in a group of males (n = 155) occupationally exposed (between 1945 and 1971) to benzidine at two chemical plants in Osaka, Japan.

Continued...

A significant ($p < 0.05$) SMR for bladder cancer (SMR = 12.5; 2 observed/0.16 expected)[1] was reported in a group (n = 379) of hourly paid "azo-dye" employees exposed to benzidine (in addition to other chemical compounds), although the observed cases of bladder cancer occurred in men who had been previously exposed to benzidine and β-naphthylamine (former workers at the Cincinnati Chemical Works). The azo-dye workers had been employed for at least 12 months (between 1952 and 1985) at a chemical plant in New Jersey. Mortality in a subgroup (n = 89) of males previously employed at the Cincinnati Chemical Works was also assessed, and there was a significant ($p < 0.05$) increase in SMRs for deaths due to cancer of the bladder (SMR = 12; 3 observed/0.25 expected), kidney (SMR = 9.5; 2 observed/0.21 expected) and central nervous system (SMR = 9.1; 2 observed/0.22 expected).

A significant ($p < 0.001$) SMR (83.3; 5 observed/0.06 expected) for deaths due to bladder cancer was reported in a group of males (n = 65) employed for at least 1 month between 1922 and 1970 at a dyestuff factory in Northern Italy, who had been exposed to benzidine during its manufacture. The mean latency period was 23.4 years.

Ten deaths due to bladder cancer were identified from 1921 to 1952 in a group (number not specified) of male workers employed in the chemical industry in Britain who had been occupationally exposed to benzidine; the expected number of deaths due to bladder cancer was 0.72.

[1]SMRs for death due to all cancers (SMR = 1.9; 16 observed/8.3 expected), cancer of the stomach (SMR = 9.7; 3 observed/0.31 expected), and central nervous system (SMR = 9.1; 3 observed/0.33 expected) were also significantly ($p < 0.05$) increased.

Source: *Canadian Environmental Protection Act Priority Substances List Assessment Report: Benzidine*

1.8.3 Description of ecotoxicological properties of the chemical

Limited data on the acute toxicity of benzidine in aquatic organisms were identified. For the red shiner (*Notropis lutrensis*), a 72- and 96-h LC_{50} of 2.5 mg/L has been reported, while for the sheepshead minnow (*Cyprinodon variegatus*), the 96-h LC_{50} was 64 mg/L.

It was reported that benzidine (20 mg/L) had some (unquantified) inhibitory effect on the respiration of organisms in activated sludge while this substance was being degraded, suggesting that a metabolite or metabolites may be responsible for the observed toxicity.

No data on the toxicity of benzidine to wild mammals, birds, sediment or soil biota were identified. Because of the low accumulation of benzidine by aquatic organisms, adverse effects on aquatic-based wildlife due to decreased availability of prey are considered unlikely.

Source: *Canadian Environmental Protection Act Priority Substances List Assessment Report: Benzidine*

PART II: FINAL REGULATORY ACTION

2. FINAL REGULATORY ACTION

2.1 The chemical is: ❑ **banned** **OR** ☑ **severely restricted**

2.2 Information specific to the final regulatory action

2.2.1 Summary of the final regulatory action

The *Prohibition of Certain Toxic Substances Regulations, 2003* prohibit the manufacture, use, processing, sale, offer for sale and importation of certain toxic substances. The Regulations exempt some uses from this prohibition, which can vary from substance to substance (more detail is provided in section 2.5 of this notification).

2.2.2	**Reference to the regulatory document**	
	Prohibition of Certain Toxic Substances Regulations, 2003 (SOR/2003-99) under the *Canadian Environmental Protection Act, 1999*	
2.2.3	**Date of entry into force of the final regulatory action**	
	March 20, 2003	

2.3	**Was the final regulatory action based on a risk or hazard evaluation?**	☑ Yes	☐ No
	If yes, give information on such evaluation		

General

The *Canadian Environmental Protection Act* (CEPA) requires the Ministers of the Environment and of Health to prepare and publish a Priority Substances List that identifies substances, including chemicals, groups of chemicals, effluents and wastes that may be harmful to the environment or constitute a danger to human health. Benzidine was placed on this list and was given priority for assessment to determine whether it is "toxic" under CEPA. As benzidine was assessed under the original CEPA (CEPA was reviewed and updated in 1999), it was assessed against the definition for "toxic" as interpreted in section 11 of the 1988 Act, which states:

"a substance is toxic if it is entering or may enter the environment in a quantity or concentration or under conditions

(a) having or that may have an immediate or long-term harmful effect on the environment;

(b) constituting or that may constitute a danger to the environment on which human life depends; or

(c) constituting or that may constitute a danger in Canada to human life or health."

The assessment of whether benzidine is "toxic," as interpreted under CEPA 1988, was based on the determination of whether it enters or is likely to enter the Canadian environment in a concentration or quantities or under conditions that could lead to exposure of humans or other biota to levels that could cause harmful effects.

Data relevant to the assessment of whether benzidine is "toxic" under CEPA 1988 were identified through evaluation of existing review documents, as well as an unpublished review of the environmental behaviour and health effects of this substance prepared under contract, supplemented with information from published reference texts and literature identified through on-line searches (from 1965 to 1992) of various databases. In addition, a number of provincial authorities were requested to provide any available information on the levels of benzidine in the drinking water of their provinces. The Quebec Ministry of the Environment was requested to provide available quantitative data on potential release of this substance from petrochemical facilities. Data relevant to the assessment of the effects of benzidine on the environment and human health obtained after November 1992 and February 1993, respectively, were not considered for inclusion.

Review articles were consulted where appropriate. However, all original studies that form the basis for determining whether benzidine is "toxic" under CEPA 1988 have been critically evaluated by staff of Health Canada (human exposure and effects on human health) and Environment Canada (entry and environmental exposure and effects).

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The environmental sections of the assessment report were reviewed by Drs. C.M. Auer and W.H. Farland of the U.S. Environmental Protection Agency. Sections related to the assessment of effects on human health were approved by the Standards and Guidelines Ruling Committee of the Bureau of Chemical Hazards of Health Canada.

Specific

Entry into the Environment

No conclusive data on the environmental release of benzidine in Canada were identified. It can enter the environment from any stage in the production, storage, transport, use and disposal of benzidine itself or benzidine-containing materials (such as dyes and pigments), or possibly by atmospheric and water-borne transport from other countries. In water, benzidine can be produced by the photodegradation of 3,3'-dichlorobenzidine. No information on the extent to which benzidine may be formed and released into the environment by this mechanism was identified.

Exposure-related Information

Fate

Oxidation, photochemical transformation, partitioning to sediment or soil, and microbial degradation are expected to be the main pathways of distribution and transformation of benzidine in the environment. Benzidine is not expected to persist in the environment, with overall half-lives in water, soil and air of less than a few weeks. The products formed by the degradation of this substance have not been well characterized.

Benzidine is expected to be slightly volatile (from water), based on its low Henry's law constant of 2.2×10^{-2} Pa m^3/mol. In water, although oxidation (by hydroperoxyl radical or molecular oxygen), biodegradation and photolysis may be significant processes, the most important process controlling the fate of benzidine appears to be oxidation by naturally occurring metal cations; the half-life is approximately a few hours. Benzidine is quickly absorbed into clays and subsequently oxidized. Although the environmental fate of such complexes is not known with certainty, it is assumed that further oxidation would be facile. Estimated half-lives for the biodegradation of benzidine in surface water and groundwater are 31 to 192 h and 96 to 384 h, respectively.

Benzidine is quickly bound in soils and sediments; however, information on the bioavailability of such bound residues was not identified. It was noted that benzidine adsorption to soil or sediment was favoured by low pH, and highly correlated with the surface area of the soil or sediment. In soil, benzidine is degraded microbially. The half-life of benzidine was estimated to be 48 to 192 h for aerobic degradation.

In air, benzidine is expected to photooxidize moderately rapidly, with an estimated half-life ranging from 0.3 to 3.2 h.

Concentrations

Benzidine was not detected (detection limit = 2 mg/L) in 34 samples of raw and 1 015 samples of treated drinking water obtained in the province of Alberta between 1987 and 1991. No other data on the concentrations of benzidine within Canada in drinking water, surface water, groundwater, air, biota, soil or sediment, foodstuffs or products containing dyes derived from this substance were identified.

In the United States, benzidine was not detected in a survey of biota and sediment; however, it was detected (but not quantitated) in 1.1% of 1 235 samples of industrial effluent and 0.1% of 879 samples of natural water collected between 1980 and 1982.

Continued...

Benzidine accumulates only moderately in aquatic biota. Bioconcentration factors (after 3 days) were 55 for mosquito fish (*Gambusia affinis*), 293 for *Daphnia magna*, 456 for mosquito larva (*Culex pipiens quinquefasciatus*), 645 for snail (*Physa* sp.) and 2 617 for a filamentous green alga (*Oedogonium cardiacum*). A 5-day bioaccumulation factor in activated sludge of 1 200, a 1-day bioaccumulation factor in algae (*Chlorella fusca*) of 850, and a 3-day bioaccumulation factor in fish (golden orfe, *Leuciscus idus melanotus*) of 83 were reported. While some of the results may suggest some potential for the bioaccumulation of benzidine by predator organisms, none has been observed, nor would it be expected for a chemical with a log octanol-water partition coefficient of 1.34.

Assessment of Benzidine under the *Canadian Environmental Protection Act* (CEPA)

Environment
The most sensitive species of fish identified is the red shiner (*Notropis lutrensis*) with a 72- and 96-hour LC_{50} of 2.5 mg/L. This concentration was divided by a factor of 20 to convert it to a chronic no-observed-effect-level, to account for interspecies differences and to extrapolate laboratory results to the field. This yielded an estimated effect threshold of 0.13 mg/L. Since benzidine is not currently produced in or imported into Canada, and since its half-life in environmental media is less than a few weeks, concentrations of benzidine in surface water in the range of the estimated effect threshold are considered very unlikely.
Therefore, on the basis of the limited available data, benzidine is not considered to be "toxic" to the environment.

Environment on Which Life Depends
Benzidine is expected to be slightly volatile and to photooxidize rapidly in air. Therefore, this substance is not expected to contribute to ozone depletion, global warming or the formation of ground-level ozone.

Therefore, on the basis of available data, benzidine is not considered to be "toxic" to the environment on which life depends.

Human Life or Health
Population Exposure
Quantitative data on the concentrations of benzidine in air, drinking water, soil or foodstuffs within Canada (or elsewhere) were not identified. Consequently, the available data are inadequate to estimate the exposure of the general population of Canada to benzidine.

Effects
The results of a number of analytical epidemiological studies as well as supporting data from case reports and series of workers occupationally exposed to benzidine have provided clear evidence for the carcinogenicity of this substance in humans. Indeed, the observed association between the occurrence of bladder carcinoma and occupational exposure to benzidine fulfils the traditional criteria (consistency, strength, specificity, temporal relationship, exposure-response relationship and plausibility) for assessment of causality in epidemiological studies.

The observed associations have been very specific, in that occupational exposure to benzidine has been associated with an increased incidence of, or death due to, cancer of the bladder—almost exclusively, transitional cell carcinoma. The results have been remarkably consistent, with an association between occupational exposure to benzidine and an increased incidence of, or mortality due to, bladder cancer observed in all the analytical epidemiological studies in which these relationships were examined.

The association between the increased incidence of, or mortality due to, bladder carcinoma is strong. Reported standardized incidence ratios (SIRs) for bladder cancer in occupationally exposed workers are 3.4 and 19.2. Reported standardized mortality ratios (SMRs) for death due to bladder cancer in occupationally exposed workers range from 12 to 83.3.

Continued...

Although quantitative information on exposure to benzidine was not assessed in any of the available analytical epidemiological studies, a relationship between qualitative measures of exposure and an increased incidence of bladder cancer was reported in two studies. Although the data are limited, there is evidence indicating that a reduction in the (occupational) exposure to benzidine was associated with a decrease in the incidence of bladder carcinoma.

The carcinogenicity of benzidine in humans is plausible, based on the overwhelming evidence of the genotoxicity of this substance. Moreover, the carcinogenicity of benzidine in experimental animals (i.e., rats, mice, hamsters) has been well documented.

Since the observed association of bladder cancer (predominantly transitional cell carcinoma) with occupational exposure to benzidine fulfils the traditional criteria for assessment of causality in epidemiological studies, on the basis of the available data, benzidine has been classified in Group I (Carcinogenic to Humans) of the classification scheme developed for the determination of "toxic" to human life or health under CEPA.

For such substances, where possible, estimated total daily intake by the general population in Canada is compared to quantitative estimates of carcinogenic potency to characterize risk and provide guidance for further action (i.e., analysis of options to reduce exposure). Owing to the lack of available information on concentrations of benzidine in environmental media to which humans are exposed, it is not possible to quantitatively estimate the total daily intake of this substance by the general population of Canada. Consequently, estimates of total daily intake have not been compared to quantitative estimates of cancer potency, although such values would be expected to be low owing to the lack of reported use of this substance in Canada.

Benzidine has been classified as being "Carcinogenic to Humans", and is therefore considered to be "toxic" to human life or health.

This approach is consistent with the objective that exposure to non-threshold toxicants should be reduced wherever possible, and obviates the need to establish an arbitrary *de minimis* level of risk for determination of "toxic" under CEPA.

Overall Conclusion
Based on the available data, benzidine is not considered to be "toxic" to the environment or the environment on which life depends. Benzidine is considered to be "toxic" to human life or health.

Reference to the relevant documentation
Canadian Environmental Protection Act Priority Substances List Assessment Report: Benzidine

2.4	Reasons for the final regulatory action	
2.4.1	**Is the reason for the final regulatory action relevant to the human health?**	☑ Yes ☐ No

If yes, give summary of the known hazards and risks presented by the chemical to human health, including the health of consumers and workers

Benzidine has been shown to cause cancer in occupationally exposed workers and experimental animals and is considered to be a "non-threshold toxicant" (i.e., a substance for which there is believed to be some chance of adverse effect at any level of exposure).

Note: Benzidine dihydrochloride is also being addressed in the Regulations because it dissociates in water into benzidine.

Reference to the relevant documentation
Canadian Environmental Protection Act Priority Substances List Assessment Report: Benzidine

Expected effect of the final regulatory action
Current levels of use of benzidine and benzidine dihydrochloride in Canada do not pose a threat to human health and the environment. The Regulations were put in place as a precautionary measure to protect the health of Canadians and ecosystems by ensuring that future production, importation and use of benzidine and benzidine dihydrochloride is prohibited with very limited exemptions.

2.4.2	**Is the reason for the final regulatory action relevant to the environment?**	❑ Yes ☑ No
	If yes, give summary of the known hazards and risks to the environment	
	Reference to the relevant documentation	

	Expected effect of the final regulatory action	

2.5	**Category or categories where the final regulatory action has been taken**	
2.5.1	**Final regulatory action has been taken for the chemical category**	☑ **Industrial**
	Use or uses prohibited by the final regulatory action	
	The *Prohibition of Certain Toxic Substances Regulations, 2003* prohibit the manufacture, use, sell, offer for sale or import of benzidine and bezidine dihydrochloride, with the exceptions listed below.	
	Use or uses that remain allowed	

	The *Prohibition of Certain Toxic Substances Regulations, 2003*, do not apply in respect of the use of benzidine or benzidine dihydrochloride:
	• in a laboratory for scientific research,
	• as a laboratory analytical standard, or
	• in the following permitted uses:
	  • staining for microscopic examination, such as immunoperoxidase staining, histochemical staining or cytochemical staining
	  • reagent for detecting blood in biological fluids
	  • niacin test to detect some microorganisms
	  • reagent for detecting chloralhydrate in biological fluids.
	
	The Regulations also do not apply in respect of the manufacture, sale, offering for sale or import of benzidine or benzidine dihydrochloride for those uses.	

2.5.2	**Final regulatory action has been taken for the chemical category**	❑ **Pesticide**
	Formulation(s) and use or uses prohibited by the final regulatory action	
	Formulation(s) and use or uses that remain allowed	

2.5.3 Estimated quantity of the chemical produced, imported, exported and used, where available.		
	Quantity per year (MT)	**Year**
Produced	6.0×10^{-11}	1995 & 1996
Imported	0	1995 & 1996
Exported	0	1995 & 1996
Used	0	1995 & 1996

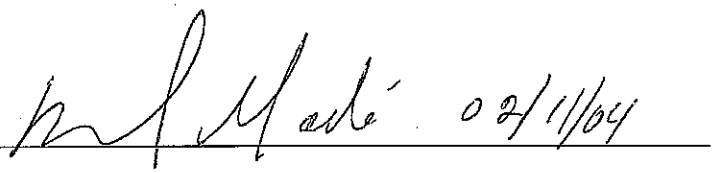
2.6	**Indication, to the extent possible, of the likely relevance of the final regulatory action to other states and regions**

2.7	**Other relevant information that may cover:**
2.7.1	**Assessment of socio-economic effects of the final regulatory action**
	Given the limited use of benzidine and its salt, the prohibition was expected to result in negligible costs to the private sector. Incremental compliance costs associated with implementing exposure and/or release controls for exempted uses are expected to be negligible since affected firms (hospitals, universities and private laboratories) are already implementing such controls as part of good laboratory practices.

2.7.2	**Information on alternatives and their relative risks**
	Benzidine was an important chemical in the manufacture of dyes some years ago, but is no longer used by the industry in North America. It has been replaced by benzidine congeners, which are chemically related compounds. Reference: Strategic Options for the management of toxic substances: Benzidine and 3,3-Dichlorobenzidine, Report of Stakeholder Consultations.
2.7.3	**Relevant additional information**
	No additional information

PART III : GOVERNMENT AUTHORITIES

Ministry/Department and authority responsible for issuing/enforcing the final regulatory action	
Institution	Environment Canada Environmental Protection Service Pollution Prevention Directorate Chemicals Control Branch
Address	Place Vincent Massey 351 St. Joseph Blvd., 12th Floor Gatineau, Quebec K1A 0H3 CANADA
Telephone	(819) 994-3648
Telefax	(819) 994-0007
E-mail address	Bernard.Made@ec.gc.ca
Designated National Authority	
Institution	Environment Canada Environmental Protection Service Pollution Prevention Directorate Chemicals Control Branch
Address	Place Vincent Massey 351 St. Joseph Blvd., 13th Floor Gatineau, Quebec K1A 0H3 CANADA
Name of person in charge	Bernard Madé
Position of person in charge	Director, Chemicals Control Branch
Telephone	(819) 994-3648
Telefax	(819) 994-0007
E-mail address	Bernard.Made@ec.gc.ca

Date, signature of DNA and official seal:  02/11/04

Interim Secretariat for the Rotterdam Convention on the Prior Informed Consent Procedure for Certain Hazardous Chemicals and Pesticides in International Trade

UNEP

FORM FOR NOTIFICATION OF FINAL REGULATORY ACTION TO BAN OR SEVERELY RESTRICT A CHEMICAL

IMPORTANT: See instructions before filling in the form

COUNTRY: JAPAN

PART I: PROPERTIES, IDENTIFICATION AND USES

1.	IDENTITY OF CHEMICAL	
1.1	**Common name**	Benzidine and its salts
1.2	**Chemical name according to an internationally recognized nomenclature (e.g. IUPAC), where such nomenclature exists**	4,4'-Diaminobiphenyl
1.3	**Trade names and names of preparations**	4,4'-Diaminobiphenyl; 4,4'-Diphenylenediamine; 4,4'-Biphenyldiamine; 4,4'-Bianiline; p-Diaminobiphenyl; 1,1'-Biphenyl-4,4'-Diamine; 4,4'-diamino-1,1'-biphenyl; fast corinth base b; p-benzidine; benzidine base; C. I. azoic diazo component 112; C. I. 37225; Benzidine
1.4	**Code numbers**	
1.4.1	**CAS number**	92-87-5
1.4.2	**Harmonized System customs code**	
1.4.3	**Other numbers (specify the numbering system)**	UN 1885 RTECS DC9625000

1.5	**Indication regarding previous notification on this chemical, if any**
1.5.1	☐ This is a first time notification of final regulatory action on this chemical.
1.5.2	☐ This is a modification of a previous notification of final regulatory action on this chemical. The sections modified are: _____ ☑ This notification replaces all previously submitted notifications on this chemical.
	Date of issue of the previous notification: September 24, 1999

PLEASE RETURN THE COMPLETED FORM TO:

Interim Secretariat for the Rotterdam Convention
Plant Protection Service
Plant Production and Protection Division, FAO
Viale delle Terme di Caracalla
00100 Rome, Italy

Tel: (+39 06) 5705 3441
Fax: (+39 06) 5705 6347
E-mail: pic@fao.org

OR

Interim Secretariat for the Rotterdam Convention
UNEP Chemicals

11-13, Chemin des Anémones
CH – 1219 Châtelaine, Geneva, Switzerland

Tel: (+41 22) 917 8183
Fax: (+41 22) 797 3460
E-mail: pic@unep.ch

1.6 Information on hazard classification where the chemical is subject to classification requirements

International classification systems	Hazard class
IARC	Group1 human carcinogen

Other classification systems	Hazard class
NTP(US)	A: Known to be a human carcinogen
EU	Category1: Substances known to be carcinogenic to man.

1.7 Use or uses of the chemical

1.7.1 ☐ **Pesticide**

Describe the uses of the chemical as a pesticide in your country:

1.7.2 ☑ **Industrial**

Describe the industrial uses of the chemical in your country:

For dyestuffs before regulated.

1.8 Properties

1.8.1 Description of physico-chemical properties of the chemical

Mp 128℃ bp 401.7℃ sp gr 1.25 sparingly soluble <0.1g/100mL at 22℃
White or reddish crystalline powder, turns dark on exposure to air and light

1.8.2 Description of toxicological properties of the chemical

Confirmed human carcinogen

1.8.3 Description of ecotoxicological properties of the chemical

PART II: FINAL REGULATORY ACTION

2.	FINAL REGULATORY ACTION			
2.1	The chemical is:	☑ banned	OR	☐ severely restricted
2.2	Information specific to the final regulatory action			
2.2.1	Summary of the final regulatory action			
	Ban on use and import			
2.2.2	Reference to the regulatory document			
	Industrial Safety and Health Law article 55 and Enforcement Order of Industrial Safety and Health Law article 16			
2.2.3	Date of entry into force of the final regulatory action			
	October 1, 1972			

2.3	Was the final regulatory action based on a risk or hazard evaluation?	☐ Yes	☑ No
	If yes, give information on such evaluation		
	Reference to the relevant documentation		

2.4	Reasons for the final regulatory action		
2.4.1	Is the reason for the final regulatory action relevant to the human health?	☑ Yes	☐ No
	If yes, give summary of the known hazards and risks presented by the chemical to human health, including the health of consumers and workers		
	Confirmed human carcinogen		
	Reference to the relevant documentation		
	IARC monograph Vol. 29, Suppl. 7; 1987, NTP 8th report		
	Expected effect of the final regulatory action		
	Prevention of occupational cancer		

2.4.2	Is the reason for the final regulatory action relevant to the environment?	☐ Yes ☑ No
	If yes, give summary of the known hazards and risks to the environment	
	Reference to the relevant documentation	
	Expected effect of the final regulatory action	

2.5	Category or categories where the final regulatory action has been taken	
2.5.1	Final regulatory action has been taken for the chemical category	☑ Industrial
	Use or uses prohibited by the final regulatory action	
	All uses	
	Use or uses that remain allowed	
	n/a	

2.5.2	Final regulatory action has been taken for the chemical category	☐ Pesticide
	Formulation(s) and use or uses prohibited by the final regulatory action	
	Formulation(s) and use or uses that remain allowed	

2.5.3 Estimated quantity of the chemical produced, imported, exported and used, where available.		
	Quantity per year (MT)	Year
Produced	n/a	
Imported	n/a	
Exported	n/a	
Used	n/a	

2.6	Indication, to the extent possible, of the likely relevance of the final regulatory action to other states and regions

2.7	Other relevant information that may cover:	
2.7.1	Assessment of socio-economic effects of the final regulatory action	

2.7.2	Information on alternatives and their relative risks	
2.7.3	Relevant additional information	

PART III : GOVERNMENT AUTHORITIES

Ministry/Department and authority responsible for issuing/enforcing the final regulatory action	
Institution	Ministry of Health, Labour and Welfare
Address	1-2-2 kasumigaseki Chiyoda-ku Tokyo 100-8916, Japan
Telephone	+81-3-3502-6756
Telefax	+81-3-3502-1598
E-mail address	
Designated National Authority	
Institution	Global Environment Division Ministry of Foreign Affairs
Address	2-2-1 Kasumigaseki, Chiyoda-ku, Tokyo 100-8919, Japan
Name of person in charge	Mr. Koichi Ito
Position of person in charge	Director
Telephone	+81-3-5501-8245
Telefax	+81-3-5501-8244
E-mail address	koichi.ito@mofa.go.jp

Date, signature of DNA and official seal: 01.09.2004. 伊藤康

MINISTRY OF FOREIGN AFFAIRS · JAPAN ·