



COSMETIC INGREDIENT HOTLIST UPDATE
Risk Assessment Division
Consumer and Hazardous Products Safety Directorate (CHPSD)

Proposed Hotlist Update:

Basic Violet 4 (BV4; CAS RN 2390-59-2)

Basic Blue 7 (BB7; CAS RN 2390-60-5)

Date Approved: 2024-11-22

EXECUTIVE SUMMARY

Basic Violet 4 (BV4) and Basic Blue 7 (BB7) were reviewed in response to the published final Chemicals Management Plan (CMP) assessment of the Triarylmethanes Group. The assessment of BV4 and BB7 detailed a high hazard flag for health concerns based on their potential carcinogenicity. In addition to the endpoints described in the CMP assessment, local effects such as eye/skin irritation and skin sensitization were considered in this assessment.

The available data, including updated cosmetic notification information, the CMP assessment, and assessments conducted in other jurisdictions were reviewed. It is recommended to add BV4 and BB7 to the Hotlist with the following conditions:

A prohibition for use in hair styling products is warranted. (both BV4 and BB7)

It is also recommended that the following product categories be restricted to the respective concentration limits:

0.4% in hair dyes (both BV4 and BB7)

0.2% in rinse-off shampoo and conditioner (both BV4 and BB7)

0.8% in nail polish (only BB7)

3% in solid bath products (only BB7)

Exposures were based on historical use for each substance and as such, those uses were the only ones assessed. Given their history and function in cosmetics, BV4 and BB7 are not anticipated to be used in other product categories.

1.0 BV4 AND BB7 IN COSMETICS

The reported function for both BV4 and BB7 is as a hair colourant (PCPC 2023).

There currently is no specific entry on the Hotlist for either substance. BV4 and BB7 may be considered coal tar dyes (Diamante *et al.* 2009; [CFTA list](#)). Coal tar dyes are included on the Hotlist and in the Cosmetic Regulations. They are prohibited for use in the area of the eye due to serious potential for eye damage, and restricted in hair dyes based on skin irritation and sensitization concerns. Although BV4 and BB7 may chemically meet the definition of a coal tar dye, as per Section 3.0 below, no relevant information was found on the irritation or sensitization potential of either dye.

Both substances are prohibited in cosmetics when used as part of hair dye products in the European Union (EU). They are not considered safe for hair dying unless they are endorsed with an adequate safety dossier. To date, no dossiers have been submitted for either substance. This comes from a “blanket prohibition” of several hair dye substances based on the Scientific Committee on Cosmetic Products and Non-Food Products (SCCNFP) opinions ([2001](#), later updated in 2004a) and potential carcinogenicity concerns, particularly bladder cancer. A strategy established after the original 2001 opinion included prioritizing the risk assessment of hair dyes and the requirement for additional data to be submitted (SCCNFP 2002). In September 2003, a list was published flagging substances for which safety dossiers had not been submitted; this led to the banning of several substances (SCCNFP 2004b).

An updated summary of cosmetic notifications was generated in May 2024 for BV4 and BB7. There were limited hits for both substances over a 5-year search period; BV4 had 6 notifications and BB7 had 18. As such, the results of historical searches¹ are summarized below. Both substances have been notified in fewer than 100 cosmetics historically, with the majority of products being hair dyes notified at 3% or less. See notes in Section 5.0 for further information on the notifications for hair dyes. The primary exposure is through the dermal route. There were no products intended for lips or eyes, nor were there any products notified as sprays or aerosols. Note that there were no shaving or fragrance products, despite these categories being selected upon notification; rather, these were solid / semi-solid bath products.

Table 1- Cosmetic Notification Search Results BV4: Historical, up to May 2024

[Redacted for confidentiality]

Table 2- Cosmetic Notification Search Results BB7: Historical, up to May 2024

[Redacted for confidentiality]

2.0 CMP ASSESSMENT AND CONCLUSIONS

The Government of Canada assessed BV4 and BB7 under the CMP as part of the [Triarylmethanes Group](#). It was concluded that BV4 and BB7 did not meet CEPA s. 64(c) toxic to human health criteria. However, both substances are considered to have a health effect of concern based on their potential carcinogenicity. Although exposures at the time of the assessment were not a concern at current levels, there may be a concern for human health if exposures were to increase. [Redacted]

A quantitative risk assessment for cancer risk was conducted for dermal cosmetic exposures for the CMP assessment. The lower 95% confidence limit for the benchmark dose of 10% extra risk (BMDL₁₀) of 16.8 mg/kg bw/day was used as the point of departure (POD). This POD was based on increased hepatocellular carcinomas in female mice fed an analogue substance (Basic Violet 3 (BV3)). For dermal penetration, the maximum flux (J_{max}) approach was used. Hair dyes were the only cosmetics quantified for BV4 (at 0.1%) and BB7 (at 0.03%) based on notification data available at that time. Exposures for BV4 were refined and adjusted to lifetime average daily doses (LADDs). Exposures for BB7 did not warrant further refinement and were therefore expressed as daily systemic values. Calculated margins of exposure (MOE)s were considered adequate and ranged from 13,000 for BV4 to 32,000–96,000 for BB7, where an MOE greater than 10,000 was considered acceptable.

Refer to Appendix 1 for more details on the studies used to determine the critical effect levels and the risk characterization approach taken for the CMP assessment.

¹ [Redacted]

3.0 TOXICOLOGICAL INFORMATION AND OTHER AVAILABLE ASSESSMENTS

The Cosmetic Ingredient Review (CIR) Expert Panel assessed BV4 and concluded that due to carcinogenic potential, there was insufficient data to support its safety for use in cosmetics. The CIR recommended that dermal absorption data and a full risk assessment are needed to complete a safety evaluation (Diamante *et al.* 2009).

The Accelerated Assessment of Industrial Chemicals (ASIC) in Australia (2015) has conducted a human health tier II assessment on a group of dyes, including BV4 and BB7. It was concluded, based on a group assessment and analogue data, that further risk management is required due to high acute toxicity, carcinogenicity, repeated dose toxicity and serious eye damage. It was recommended that all the substances in the group be listed in Schedule 4 of the Poisons Standard. CAS numbers for both BV4 and BB7 are currently included in [Schedule 4, 6 and 10](#).

The European Food Safety Authority (EFSA) published a scientific report ([2017](#)) on dyes used in aquaculture, including BB7. Although the scope of the assessment is not relevant to cosmetic exposure, the EFSA determined that BB7 is not a high potency carcinogen. However, it should be regarded as genotoxic (based on computational toxicity and modeling). It was also determined that there was no safety concern with respect to allergy for BB7.

Assessments under CMP typically focus on systemic toxicity and repeated dose exposures. Acute toxicity and local effects, such as irritation and sensitization, were not included in the CMP assessment for BV4 and BB7. These endpoints, however, are relevant and need to be considered when developing potential conditions for the Hotlist.

Acute Toxicity: Two acute oral studies were located for BV4; an oral rat LD₅₀ of 308 mg/kg (female), 549 mg/kg (male) (Diamante *et al.* 2009), and an oral approximate lethal dose in deer mice of 320 mg/kg (Schafer and Bowles 1985). There was no dermal or inhalation data located for BV4, and no data (any route) were located specifically for BB7.

Irritation and Sensitization: There was no relevant information located for either substance.

4.0 ANALOGUE – BASIC VIOLET 3

BV3 was used in the CMP assessment as an analogue for BV4 and BB7. BV3 is similar to BV4 and BB7 with respect to physical-chemical properties and chemical structure. In addition to similarities in the chemical structure and physical-chemical properties, the applicability of BV3 data to characterize the carcinogenic potential of BV4 and BB7 was supported by similarities in their chemical profiles and (Q)SAR model predictions. Further, metabolic pathways predicted by modeling indicate that BV4 and BB7 may undergo the same metabolic transformations as BV3 (ECCC, HC 2020).

Other jurisdictions have also similarly used BV3 analogue data for assessing BV4 and/or BB7 in group assessments. The CIR assessed BV3 as part of the grouping with BV4 and it resulted in the same conclusions as summarized above for BV4 (Diamante *et al.* 2009). Similarly, BV3 was also part of the group assessment conducted by ASIC (2015), where the majority of the available toxicity data used in

the assessment were from BV3. The same ASIC risk management actions as cited above for BV4 and BB7 also apply to BV3. Finally, BV3 was also included in the EFSA scientific report (2017) and the same overall conclusions as summarized above for BB7 were determined for BV3.

Since the CMP assessment, the International Agency for Research on Cancer (IARC 2022) has published an evaluation of BV3. Although the publication is recent, the key data considered in the assessment are not novel from what was available at the time of the CMP assessment. IARC concluded that there is inadequate evidence in humans regarding the carcinogenicity of gentian violet (a synonym for BV3) and there is sufficient evidence in experimental animals regarding the carcinogenicity of gentian violet. There is limited mechanistic evidence. This resulted in an overall evaluation into Group 2B (i.e. possibly carcinogenic to humans).

BV3 has been prohibited on the Hotlist since 2003 due to cancer and mutagenicity concerns. BV3 is also prohibited in EU and there were no EU Scientific Committees on Consumer Safety (SCCS) reports or opinions located.

Health Canada published an [Information Update](#) for gentian violet (HC 2019a), *“After completing two safety assessments, the Department concluded that, as with other known cancer causing substances, there is no safe level of exposure, and therefore any exposure to these drug products is a potential cause for concern”*. Based on the supporting [Summary Safety Review for gentian violet](#) (HC 2019b), Health Canada conducted two risk assessments, one for a medical device (a foam dressing) and one for a topical non-prescription drug. An FAO/WHO Joint Expert Committee on Food Additives (JECFA) (2014) assessment concluded that the substance alters genetic material and causes cancer, and that no acceptable daily intake could be established. Based on that, the WHO Codex Alimentarius Commission (2018) recommended that exposures to the substance as residue in foods should be prevented. This in turn what triggered the Health Canada review. Note that this 2019 Health Canada review was independent of the work conducted under the CMP. Furthermore, the CMP assessment does cite and take into consideration the JECFA 2014 assessment; it is the source of the POD used for assessing cancer risk in the CMP assessment. [Redacted]

Since there was no irritation or sensitization toxicity data available for either BV4 or BB7, information on these endpoints for BV3 is summarized below.

Irritation: The available information suggests that BV3 is at most a mild skin irritant. There is a report of mild irritation in humans, however details were limited. An animal study in rabbits reported no irritation after a 24-hour exposure period (ECHA 2023).

BV3 has been reported to cause severe and irreversible eye irritation in rabbits at full strength as well as at low concentration (1%) with repeated exposures. A no-effect concentration of 0.25 mg/ml has been suggested. However, in another study, at 10% dilution after a single exposure, eye irritation in rabbits was mild to very mild. One report in humans was located, a 1% solution of BV3 was considered highly irritating following an accidental medical procedure (purposeful administration directly into eye) (ECHA 2023; Diamante *et al.* 2009).

Sensitization: BV3 was not sensitizing in a guinea pig study (ECHA 2023). There is some limited indication of sensitization in humans, however this is in patch testing studies where concentrations are typically 2% in water (Diamante *et al.* 2009).

5.0 QUANTITATIVE RISK ASSESSMENT FOR HOTLIST RECOMMENDATION

Selection of critical health endpoint: A BMDL₁₀ of 16.8 mg/kg bw/day was selected as the most sensitive endpoint for BV4 and BB7, based on carcinogenicity of the analogue BV3. In line with the CMP assessment, this POD is based on increased hepatocellular carcinomas in female mice. Given the lack of significant acute toxicity, skin irritation or sensitization, a separate endpoint for these local effects is not necessary. Eye irritation, based on information on the analogue BV3, has been reported, however details were limited and there are currently no notified products intended specifically for use in the area of the eye. Furthermore, limits set based on the carcinogenicity endpoint would be protective of concentrations resulting in eye irritation.

Dermal absorption value: A dermal absorption value of 50% was selected. This value is the default used by the SCCS (2023) when experimental data are lacking or inadequate for a substance. There were no experimental dermal absorption data located for BV4, BB7 or the analogue BV3. The properties of BV3 and BB7 suggest that dermal absorption would not be favorable, i.e. molecular weights are close to or above 500 g/mol and log k_{ow} values are greater than 4.5. Other sources also hypothesize that dermal penetration would be slow due to the large quaternary ammonium ions (Diamante *et al.* 2009; ASIC 2015). Overall, this suggests that a dermal absorption value of 50% is a conservative estimate.

Exposure scenarios: Default exposure values were taken from the current (as of December 2023) Personal Care Products (PCP) workbook. Note that many of these default values have been updated since the CMP assessment was published. Because the critical health endpoint is carcinogenicity, the daily systemic exposures were refined to lifetime average daily dose (LADD).

Current notification data were examined, and several scenarios were considered. Hair dyes made up the majority of notifications, however other use scenarios were also assessed (shampoo, conditioner, bath products, nail products and hair styling products).

For hair dyes, there are two categories for cosmetic notification: (a) hair colour – permanent and (b) hair colour – temporary. The intention of the temporary category is to represent “one-time” hair colours, where the dye does not penetrate into the hair, such as those that you might apply for a costume that wash out after 1-2 shampoos. Having examined the products notified with BV4 or BB7 under these two product categories, it is evident that those noted as temporary colours are actually permanent colours, i.e. intended to last more than 1-2 washes. Or alternatively, several notified as temporary hair colour are more appropriately described as shampoos, conditioners or mousses for coloured hair and have been assessed under those categories. Furthermore, and more importantly, there are different default exposure values in the PCP workbook for 3 hair dye categories: (a) temporary hair dyes (b) permanent hair dyes and (c) semi-permanent hair dyes. Permanent hair dyes are two component dyes that require an oxidizer. Only one of the notified products, from 2002, mentions the use of an oxidizer and there is no evidence that this product is still being marketed. Therefore, based on available information on more

recent notifications, it is assumed that these substances are not used in permanent dyes. Default values for semi-permanent hair dyes were applied for the purposes of establishing the proposed maximum concentrations.

The notified shampoos, conditioners and styling products were all intended for use on colour treated hair and therefore only teens and adults were considered, as was the case for hair dyes as well. Furthermore, the notified styling products were all foam mousses; other hair styling products were not considered. The dermal route of exposure was the only route considered, based on use patterns of the notified products. There were no products notified that would suggest ingestion or inhalation would contribute significantly to exposures.

Target MOE: In line with the CMP assessment, an MOE of 10 000 was considered as the maximum acceptable value for calculating threshold concentrations. A risk level of 1 in 10 000 is typically the minimum level of protection for carcinogens.

Maximum concentration producing an adequate MOE: Refer to Appendix 2 for additional details, the work done for hair dyes is shown as an example. Maximum concentrations were calculated for several cosmetic scenarios based on current notification data:

Hair dye (semi-permanent) = 0.44%
Shampoo = 0.24%
Rinse-off conditioner = 0.22%
Nail polish = 0.87%
Bath product (solid) = 3.39%
Hair styling product (foam mousse) = 0.04%

6.0 CONCLUSIONS AND RECOMMENDATIONS

BV4 and BB7 are not currently included on the Hotlist. The assessment conducted under the CMP as well as those published by other jurisdictions were taken into consideration to develop this document.

Based on the quantitative assessment and the approach described in this document, and in line with the CMP assessment, CHPSD recommends that Basic Violet 4 (CAS RN 2390-59-2) and Basic Blue 7 (CAS RN 2390-60-5) be added to the Hotlist with concentration restrictions of:

- 0.4% in hair dyes (both BV4 and BB7)
- 0.2% in rinse-off shampoo and conditioner (both BV4 and BB7)
- 0.8% in nail polish (only BB7)
- 3% in solid bath products (only BB7)

Furthermore, because the maximum concentration calculated for hair styling products is considerably less than the notified concentrations, CHPSD recommends that a prohibition for this product category may be warranted for both substances.

Exposures were based on historical use and as such, those uses were the only ones assessed. Given their history and function in cosmetics, BV4 and BB7 are not anticipated to be used in other product categories.

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APPENDIX 1: EXCERPTS FROM CMP ASSESSMENT

Information was taken from the published final Screening Assessment Report. Available: <https://www.canada.ca/en/environment-climate-change/services/evaluating-existing-substances/screening-assessment-triarylmethanes-group.html>. The complete references cited here are available at the above link.

Health Effects – Study summary for critical effect levels

In a 2-year carcinogenicity study in mice fed approximately 0, 11/14, 32/36, and 64/71 mg/kg bw/day (males/females) Basic Violet 3, increased erythropoiesis in the spleen and atrophy of ovaries in females were observed at the lowest tested dose of 14.3 mg/kg bw/day (Littlefield 1984; Littlefield *et al.* 1985). At approximately 36 mg/kg bw/day and above, there were increased liver adenomas and carcinomas in females, both of which were also increased in males at 64 mg/kg bw/day, along with increased mortality in females. In a 2-year carcinogenicity study in rats exposed to Basic Violet 3 via the diet, no adverse effects were observed at the lowest tested dose of 30/40 mg/kg bw/day (males/females). At the LOAEL of 80/100 mg/kg bw/day (males/females), there was increased mortality (males) and increased follicular cell adenoma of the thyroid gland (females), as well as increased hepatocellular adenoma in both sexes (Littlefield *et al.* 1989).

The incidence of increased hepatocellular carcinomas in female mice at 2 years was 7/185, 5/93, 30/93, or 73/95 for 0, 14, 36, or 71 mg/kg bw/day, respectively. The dose-response relationship for the two tumour types was similar (the incidence of hepatocellular adenomas in female mice at 2 years was 8/185, 8/93, 36/93, 20/95 for 0, 14, 36, or 71 mg/kg bw/day, respectively) (JECFA 2014). To determine the increased risk of hepatocellular carcinomas, JECFA (2014) used the US EPA's benchmark dose software (BMDS, version 2.2) to establish that use of the multistage model had an acceptable fit, had the lowest Akaike's Information Criterion value, and had the lowest benchmark dose value for 10% extra risk (19.9 mg/kg bw/day) and benchmark dose lower 95% confidence limit for 10% extra risk (BMDL₁₀ of 16.8 mg/kg bw/day) among the models.

Based on the structural similarity between Basic Violet 3 and Basic Violet 4, it is assumed that up to 6 or 8 mg/kg bw/day Basic Violet 4 will be unlikely to increase chromosomal aberrations or damage DNA in mice (Au and Hsu 1979; Littlefield *et al.* 1985; Aidoo *et al.* 1990; Diamante *et al.* 2009). A 2-year carcinogenicity study in mice exposed to dietary Basic Violet 3 indicates that potential effects may include increased erythropoiesis in the spleen and atrophy of the ovaries in females at 14 mg/kg bw/day and above, and increased hepatocellular tumours at 36 mg/kg bw/day and above, with a BMDL₁₀ of 16.8 mg/kg bw/day for increased risk of hepatocellular carcinomas in female mice (Littlefield 1984; Littlefield *et al.* 1985; JECFA 2014). In addition to similarities in the chemical structure and physical-chemical properties of Basic Violet 3 and Basic Violet 4, the applicability of Basic Violet 3 data to characterize the carcinogenic potential of Basic Violet 4 was supported by similarities in their chemical profiles and (Q)SAR model predictions (Derek Nexus 2016; Leadscope Model Applier 2016; OECD QSAR Toolbox 2013; Times 2016). Further, metabolic pathways predicted by Times 2016 indicate that Basic Violet 4 may undergo the same metabolic transformations as Basic Violet 3 (Docampo and Moreno 1990), which

further supports the read-across from Basic Violet 3 to Basic Violet 4 in the absence of a substance-specific carcinogenicity study.

On the basis of a 2-year carcinogenicity study in mice exposed to dietary Basic Violet 3, Basic Blue 7 is expected to increase erythropoiesis in the spleen and atrophy of the ovaries in females at 14 mg/kg bw/day and above and to increase the incidence of hepatocellular tumours at 36 mg/kg bw/day and above, with a BMDL₁₀ of 16.8 mg/kg bw/day for increased risk of hepatocellular carcinomas in female mice (Littlefield 1984; Littlefield *et al.* 1985; JECFA 2014). In addition to similarities in the chemical structure and physical-chemical properties of Basic Violet 3 and Basic Blue 7, the applicability of Basic Violet 3 data to characterize the carcinogenic potential of Basic Blue 7 was supported by similarities in their chemical profiles and (Q)SAR model predictions (Derek Nexus 2016; Leadscope Model Applier 2016; OECD QSAR Toolbox 2013; Times 2016). As in the case of Basic Violet 4, the metabolic pathways predicted by Times 2016 indicate that Basic Blue 7 may undergo the same metabolic transformations as Basic Violet 3 (Docampo and Moreno 1990), which further supports the read-across from Basic Violet 3 to Basic Blue 7 in the absence of a substance-specific carcinogenicity study.

Lifetime average daily dose (LADD)

The LADD was calculated as a refinement for dermal exposure to semi-permanent hair dye exposures to Basic Violet 4 to account for use of this product by teenagers and adults, as well as to estimate the potential cancer risk from daily exposure to Basic Violet 3 from drinking water. The assumptions and equation are provided below:

DSE: daily systemic exposure

Average lifetime (AL): 70 years (US EPA 2011)

Age group durations (AD): 0.5 years for infants (0 to 0.5 years), 4.5 years for toddlers (0.5 to 4 years), 7 years for children (5 to 11 years), 8 years for teenagers (12 to 19 years) and 50 years for adults (20+ years) (Health Canada 1998)

$$\text{LADD} = \left[\left(\text{DSE}_{\text{infant}} \times \text{AD}_{\text{infant}} \right) + \left(\text{DSE}_{\text{toddler}} \times \text{AD}_{\text{toddler}} \right) + \left(\text{DSE}_{\text{child}} \times \text{AD}_{\text{child}} \right) + \left(\text{DSE}_{\text{teen}} \times \text{AD}_{\text{teen}} \right) + \left(\text{DSE}_{\text{adult}} \times \text{AD}_{\text{adult}} \right) \right] / [\text{AL}]$$

APPENDIX 2: EXPOSURE DEFAULTS AND QRA APPROACH

The work done for hair dyes is shown here as an example. A similar process was completed for the other product categories.

Using a target MOE = 10 000 and the POD = 16.8 mg/kg bw/day, the maximum permitted exposure is 0.00168 mg/kg bw/day. Table A1 shows the defaults used for LADD calculations. Life expectancy was updated since the 2011 references used and cited in the CMP assessment (HC 2014).

Table A1 – LADD

Age group (years)	duration (years)
0-5 mo	0.5
6-11 mo	0.5
1y	1
2-3y	2
4-8y	5
9-13y	5
14-18y	5
19+y	59
average lifetime	78

Table A2 – Hair dye

	Semi-permanent Hair Dye (14-18y)	Semi-permanent Hair Dye (19+y)
amount product applied (mg)	35000	35000
Product applied frequency (per day)	0.012	0.02
retention factor RF	0.1	0.1
dermal absorption	0.5	0.5
concentration []	100%	100%
Exposure (mg/day)	21	35
POD (mg/kg bw/day)	16.8	16.8
Target MOE	10000	10000
Acceptable dose (mg/kg bw/day)	0.00168	0.00168
Body weight (kg)	62	74
Max amount (mg/day)	0.10416	0.12432

Max acceptable concentration limit (%)	0.496	0.3552
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LADD-based concentration calculations

Exposure (mg*years/kg bw/day)	1.69354839	27.9054054
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LADD (mg/kg bw/day) 0.37947377

[] for acceptable dose based on LADD (%) 0.44271835