Acetamide, N-[4-[(2-hydroxy-5-methylphenyl)azo]phenyl]-: Human health tier II assessment

13 February 2015

CAS Number: 2832-40-8

Preface

This assessment was carried out by staff of the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) using the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework.

The IMAP framework addresses the human health and environmental impacts of previously unassessed industrial chemicals listed on the Australian Inventory of Chemical Substances (the Inventory).

The framework was developed with significant input from stakeholders and provides a more rapid, flexible and transparent approach for the assessment of chemicals listed on the Inventory.

Stage One of the implementation of this framework, which lasted four years from 1 July 2012, examined 3000 chemicals meeting characteristics identified by stakeholders as needing priority assessment. This included chemicals for which NICNAS already held exposure information, chemicals identified as a concern or for which regulatory action had been taken overseas, and chemicals detected in international studies analysing chemicals present in babies' umbilical cord blood.

Stage Two of IMAP began in July 2016. We are continuing to assess chemicals on the Inventory, including chemicals identified as a concern for which action has been taken overseas and chemicals that can be rapidly identified and assessed by using Stage One information. We are also continuing to publish information for chemicals on the Inventory that pose a low risk to human health or the environment or both. This work provides efficiencies and enables us to identify higher risk chemicals requiring assessment.

The IMAP framework is a science and risk-based model designed to align the assessment effort with the human health and environmental impacts of chemicals. It has three tiers of assessment, with the assessment effort increasing with each tier. The Tier I assessment is a high throughput approach using tabulated electronic data. The Tier II assessment is an evaluation of risk on a substance-by-substance or chemical category-by-category basis. Tier III assessments are conducted to address specific concerns that could not be resolved during the Tier II assessment.

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted

and published separately, using information available at the time, and may be undertaken at different tiers.

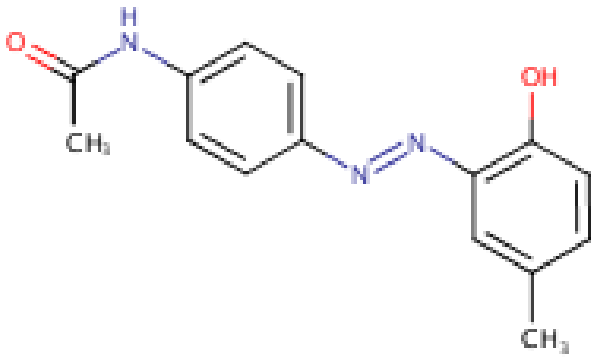
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

For more detail on this program please visit:www.nicnas.gov.au

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	C.I. Disperse Yellow 3 4-(2-hydroxy-5-methylphenylazo)acetanilide C. I. 11855 Acetate Fast Yellow G C.I. Solvent Yellow 77
Structural Formula	
Molecular Formula	C15H15N3O2
Molecular Weight (g/mol)	269.30
Appearance and Odour (where available)	Brownish-yellow powder.
SMILES	c1(O)c(N=Nc2ccc(NC(C)=O)cc2)cc(C)cc1

Import, Manufacture and Use

Australian

No specific Australian use, import, or manufacturing information has been identified.

International

The following international uses have been identified through the United States (US) National Library of Medicine's Haz-Map database and various international assessments (IARC, 1990; CIR, 1996; OEHHA, 2012; Government of Canada, 2013).

The chemical has reported cosmetic use in oxidative hair dyes. No information is available on the concentrations used. Use of the chemical in cosmetics in the United States (US) was reported in 1992, but there was no documented use in 2011 (Personal Care Product Council, 2011). The chemical is not listed in the US Personal Care Product Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary.

The chemical has reported commercial uses as a dye:

- to colour nylon, polyvinyl chloride and acrylic fibers, wools and furs, leather, cellulose acetate, polystyrene, and other thermoplastics;
- in ink products; and
- in pulp and paper manufacturing.

The dyed materials are used in products such as clothing including hosiery and carpets. In the European Union (EU), the chemical has been identified in gloves and in beige stockings and pantihose (IARC, 1990; RAPEX). The chemical has been detected in wastewater from carpet dyeing plants in the US.

Restrictions

Australian

No known restrictions have been identified.

International

The chemical is listed on the following (Galleria Chemica):

- Association of South East Asian Nations (ASEAN) Cosmetic Directive Annex II Part 1: List of substances which must not form part of the composition of cosmetic products;
- EU Cosmetics Regulation 1223/2009 Annex II—List of substances prohibited in cosmetic products; and
- New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain.

The chemical is also in the EU's list of 179 substances banned for use in hair dye products (European Commission, 2010).

Existing Work Health and Safety Controls

Hazard Classification

The chemical is listed on the Hazardous Substances Information System (HSIS) (Safe Work Australia):

- Carc Cat 3; R40 (carcinogenicity); and
- Xn; R43 (skin sensitisation).

Exposure Standards

Australian

No specific exposure standards are available.

International

No specific exposure standards are available.

Health Hazard Information

Toxicokinetics

Whilst there are no specific data available on toxicokinetics of the chemical, due to its lipophilicity and small molecular size, absorption is expected following oral, dermal and inhalation exposure (CIR, 1996; Stahlmann et al., 2006; Government of Canada, 2013). The skin sensitising properties and effects following repeated exposure support the chemical's bioavailability.

Based on data for acetanilide (CAS No. 103-84-4), deacetylation, followed by the activation of the resulting free amine is considered to be a minor metabolic pathway (OECD, 2001).

Similarly to other azo disperse dyes, the chemical is expected to be metabolised through reductive cleavage of the azo bond. This process would initially form two aromatic amines that are not listed in the Australian Inventory of Chemical Substances (AICS): 4-aminoacetanilide (CAS No. 122-80-5) and 2-amino-*p*-cresol (CAS No. 95-84-1) (CIR, 1996, OEHHA, 2012; Government of Canada, 2013). These aromatic amines are expected to have greater absorption than the dye from which they are derived (Platzek et al., 1999).

Azo bond reduction and cleavage occurs by enzyme-mediated metabolism in the liver, skin and intestines. In the liver, cytosolic and microsomal enzymes (Platzek et al., 1999), including NADH cytochrome P450 reductase, NAD(P)H quinone oxidoreductase and cytochrome P450s (OEHHA, 2012), facilitate metabolism. Bacterial strains in human faeces have been shown to cleave azo dyes, suggesting that intestinal microflora play an important role in azo bond reduction (Platzek et al., 1999).

Although azo bond reduction occurs favourably in anaerobic conditions, several in vitro and in vivo studies indicated that this process could also occur aerobically when azo dyes are applied to the skin (SCCP, 2005). In vitro, the skin microflora of mice, guinea pigs and humans caused reductive cleavage of the azo dyes, followed by percutaneous absorption (SCCNFP, 2002). In addition, non-biological processes, such as thermal and photochemical degradation, have been reported to break azo linkages (Engel et al., 2009).

Azo bond reduction of the chemical has been reported in vitro following incubation with *Bacillus subtilis* laccase. Approximately 9 % of the dye was reduced after 24 hours (Government of Canada, 2013).

Metabolically, the aromatic amine metabolites could further undergo ring oxidation, N-glucuronidation, N-acetylation, and N-oxidation (SCCNFP, 2002). The toxicity of aromatic amines can be largely influenced by N-oxidation, a process primarily

mediated by cytochrome P450 enzymes, such as CYP1A2 and CYP3A4. Other enzymes could also play a role. Under an acidic environment, the N-hydroxylamines produced from the N-oxidation process mediated by cytochrome P450s or flavin-containing monooxygenases can form reactive nitroxide radicals or nitrenium ions (SCCNFP, 2002; OEHHA, 2012). These molecules are highly reactive and are capable of DNA binding (SCCNFP, 2002; OEHHA, 2012).

Acute Toxicity

Oral

Based on the limited data available, the chemical is considered to have low acute toxicity following oral exposure. No mortality or signs of toxicity were reported following a 24-hour exposure of female B6C3F1 mice and Fischer 344 (F344) rats to a diet containing doses up to 100000 mg/kg in the diet (approximately 5000 mg/kg bw and 13000 mg kg bw for rats and mice respectively) (CIR, 1996; Government of Canada, 2013).

Dermal

No data are available.

Inhalation

No data are available.

Corrosion / Irritation

Skin Irritation

No data are available.

Eye Irritation

No data are available.

Sensitisation

Skin Sensitisation

This chemical is classified as hazardous with the risk phrase ‘May cause sensitisation by skin contact’ (R43) in the HSIS (Safe Work Australia). The positive results reported in a modified local lymph node assay (LLNA) in mice and skin patch tests in humans (see **Observation in humans** section) support this classification.

The standard and modified (sensitisation—challenge) LLNA were used to test the sensitising potential of Disperse Yellow 3 and its aromatic amine metabolites, 4-aminoacetanilide and 2-amino-*p*-cresol (Stahlmann et al., 2006). The sensitisation potential was determined by evaluating the lymph node weight and cellularity. Radioactive labelling was not used. In the standard sensitisation assay, 10 % or 30 % of each chemical (in dimethyl sulfoxide (DMSO)) was applied to the back of the left ear of female NMRI mice for three consecutive days. Disperse Yellow 3 and 4-aminoacetanilide were negative, but 2-amino-*p*-cresol showed a clear positive reaction.

However, when the protocol was modified to a sensitisation—challenge assay, all three chemicals produced sensitisation reactions. In this assay, mice were induced by applying 10 % and 30 % of the chemicals on the shaved portion (2 cm^2) of the skin at the back of the mice, once daily on days 1-3. The mice were challenged at days 15 to 17 of the assay period by applying each of the chemical at the back of each mouse ear (Stahlmann et al., 2006).

Compared with controls, significant increases in lymph node weights, cellularity and in the number of lymphocytes carrying A1 epitopes were observed in animals exposed to Disperse Yellow 3 (10 % and 30 % concentration) and 4-aminoacetanilide (30 % concentration). These indicated sensitisation reactions. However, stronger sensitisation was induced by 2-amino-*p*-cresol as demonstrated by the following: significant increases in lymph node weight; cell proliferation; relative decrease in T-cells; and a relative increase in B-cells and in 1A-positive cells at both tested concentrations (Stahlmann et al., 2006).

In an in vitro study, Disperse Yellow 3 was found to be a strong skin sensitiser in a loose-fit coculture-based sensitisation assay (LCSA) using primary human keratinocytes and peripheral blood mononuclear cells (Sonnenburg et al., 2012). The reported EC3 in this study was 0.5 (the chemical concentration required to elicit a threshold positive response).

Observation in humans

A number of reports indicate sensitisation potential of the chemical. Allergic, contact-type dermatitis was reported in individuals with exposure to textiles coloured with dyes containing Disperse Yellow 3 (IARC, 1990; HSDB). The chemical has been identified as a disperse dye known to cause occupational contact allergic dermatitis in the textile industry (OEHHA, 2012).

Epicutaneous testing of the chemical (1 % in petroleum) was conducted in 12 eczema patients with suspected contact allergy to textile dyes. The result showed that five patients had positive reactions to the chemical (CIR, 1996).

In another study, a number of patients who tested positive for the chemical were also positive for the aromatic amine metabolites 4-aminoacetanilide and 2-amino-*p*-cresol. In this study, 6/10 patients tested with a dilution series of the chemical showed positive reactions. In addition, four patients showed positive reactions at 0.01 % of the chemical. These patients also showed a positive reaction to 4-aminoacetanilide (3/6) and 2-amino-*p*-cresol (6/6) (Malinauskiene et al., 2012).

Positive results in a patch test performed with a purified form of the dye indicated that it is the chemical and not the impurities that is responsible for the sensitisation response (CIR, 1996).

In a recent review on contact dermatitis from textiles, Malinauskiene et al. (2013) reported that a considerable number of patients showed positive patch test reactions to Disperse Yellow 3 (1 % in petrolatum). Positive reponses were seen in approximately 7 % (averaged over 18 studies) of patients suspected or thought likely to have contact dermatitis caused by disperse dye allergy (aimed patch testing). In routine patch testing that included textile dyes (screening testing), a 0.8 % prevalence rate for Disperse Yellow 3 was reported (averaged over 12 studies). In Italy, the chemical was also found to be one of the prevalent contact allergens in children (Malinauskiene et al., 2013).

Repeated Dose Toxicity

Oral

Considering the no observed adverse effect level (NOAEL) available from a 13-week study in F344 rats and B6C3F1 mice (approximately 125 mg/kg bw/day and 325 mg/kg bw/day respectively), repeated oral exposure to the chemical is not considered to cause serious damage to health. In this study, rats and mice were exposed to the chemical (via diet) at doses of 1250, 2500, 5000, 10000 and 20000 ppm (CIR, 1996). Effects in rats observed at doses ≥5000 ppm (approximately 250 mg/kg bw/day) included:

- vacuolar degeneration in the pars distalis of the pituitary gland;
- fibrous thickening of the thyroid capsule and mild to moderate thyroid hyperplasia;

- mild to moderate haemosiderosis and mild lymphocytic depletion of the spleen; and
- mild to moderate pigment deposition in the cortical tubules of the kidney.

Haemosiderosis of the renal tubular epithelium and spleen and swelling of centrilobular hepatocytes were observed in mice dosed at 5000 mg/kg in the diet (650 mg/kg bw per day) (CIR, 1996).

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

Based on the weight of evidence from the available in vitro and in vivo genotoxicity studies, the chemical is considered to be genotoxic. Classification is considered to be warranted (refer **Recommendation** section).

A number of in vitro genotoxicity tests for gave positive results, and Disperse Yellow 3 also induced DNA damage in vivo (IARC, 1990; OEHHA, 2012; Government of Canada, 2103). The aromatic amine metabolites are also genotoxic in vivo and/or in vitro.

In vitro, the chemical tested positive in a *Salmonella typhimurium* reverse mutation assay in strains TA97, TA98, TA1537, TA1538, TA100 with and without metabolic activation (OEHHA, 2012). The chemical also tested positive in these strains with flavin mononucleotide (FMN) pre-incubation modification (Prival's modification method) in an *S. typhimurium* assay (Cameron et al., 1987).

In addition, the chemical tested positive in the following in vitro tests:

- chromosomal aberration (CA) in frog larvae (*Rana clamitans*);
- L5178Y mouse lymphoma cells forward mutation assay at the thymidine kinase (*tk*) locus with metabolic activation;
- sister chromatid exchange (SCE) in Chinese hamster ovary (CHO) cells with metabolic activation; and
- unscheduled DNA synthesis (UDS) in primary rat hepatocytes (CIR, 1996; OEHHA, 2012; Government of Canada, 2013).

In vivo, the chemical induced DNA damage (comet assay) in the stomach, liver and brain of mice dosed once orally at the maximum tolerated dose (MTD). The stomach, colon, liver, kidney, bladder, lung, brain, and bone marrow were sampled (Tsuda et al,. 2000; Government of Canada, 2013). Tumours were observed in carcinogenicity studies at two of the sites where DNA damage was observed (see **Carcinogenicity** section). The chemical gave negative results in a mouse micronucleus assay and in an alkaline elution assay for DNA damage in the rat liver (OEHHA, 2012).

The chemical's azoreduction metabolites (4-aminoacetanilide and 2-amino-*p*-cresol) have genotoxic/mutagenic properties. The aromatic amine, 4-aminoacetanilide, was mutagenic in vitro in *S. typhimurium* strain TA98 with metabolic activation. In vivo, 4-aminoacetanilide induced chromosomal aberrations in mouse bone marrow cells (OEHHA, 2012). The other metabolite, 2-amino-*p*-cresol, tested positive in *S. typhimurium* strains TA97 and TA100 without metabolic activation. It also induced mouse lymphoma cells (L5178Y) forward mutations with or without metabolic activation (OEHHA, 2012).

Carcinogenicity

The chemical is classified as hazardous—Category 3 carcinogenic substance—with the risk phrase ‘Limited evidence of carcinogenic effect’ (Xn; R40 in the HSIS (Safe Work Australia). The available data support this classification.

In long-term feeding studies (103 weeks), exposure to the chemical caused tumours in male F344 rats and male and female B6C3F1 mice (OEHHA, 2012). The concentrations tested in these studies were 5000 and 10000 ppm (in the diet) for rats (approximately 250 and 500 mg/kg bw/day) and 2500 and 5000 mg/kg for mice (approximately 325 and 650 mg/kg bw/day).

Based on the results, the liver was the main target organ of carcinogenicity in male rats. In these animals, dose-dependent significant increases in hepatocellular adenomas and combined hepatocellular adenomas and carcinomas were observed in treated animals. In addition, combined adenoma, mucinous adenocarcinoma and sarcoma, and combined squamous cell papilloma and fibrosarcoma were also identified in the glandular and non-glandular portions of the stomach of the exposed male rats; however, these tumours are rare. No tumours were reported in female rats (NTP, 1982; IARC, 1990; OEHHA, 2012; Government of Canada, 2013).

Compared with controls, exposure to the chemical induced alveolar/bronchiolar adenoma and combined adenoma and carcinoma of the lungs of male mice (both doses). In female mice, exposure to approximately 325 and 650 mg/kg bw/day caused significant effects in the haematopoietic system (malignant lymphoma and combined malignant lymphoma and leukaemia) and in the liver (adenoma and combined adenoma and carcinoma) (NTP, 1982; IARC, 1990; OEHHA, 2012; Government of Canada, 2013).

There is a lack of epidemiological data to indicate specific links between occupational exposure to the chemical and tumour development.

The mechanism of action underlying the chemical's carcinogenic potential is not fully understood. However, the available data suggest a genotoxic mode of action.

Reproductive and Developmental Toxicity

No data are available.

Risk Characterisation

Critical Health Effects

The chemical could be carcinogenic following long-term repeated exposure. A genotoxic mode of action cannot be excluded. The chemical, including its aromatic amine metabolites could produce skin sensitisation reactions.

Public Risk Characterisation

Cosmetic

Although use in cosmetic products in Australia is not known, the chemical has identified use in hair dye products. This use is now prohibited in some countries overseas (see **International restrictions** section). Currently, there are no restrictions in Australia on using this chemical in cosmetics. In the absence of any regulatory controls in Australia, the characterised critical health effects, including sensitisation and carcinogenicity, have the potential to pose an unreasonable risk if the chemical is used in hair dye products in Australia.

Dyed textiles and paper products

When used on synthetic fibres, the fastness of disperse dyes to the fibre is limited (Stahlmann et al., 2006). In addition there could be increased exposure if the disperse dyeing is not done in accordance with best practice (OEHHA, 2012).

Therefore the public could be exposed to the chemical by:

- dermal contact with the chemical from prolonged exposure to articles of clothing containing the dye, particularly tight fitting synthetic garments such as hosiery; and

- oral exposure by young children sucking textiles containing the dye.

If the chemical is used in paper products, sucking these products is also a potential route of exposure.

Allergic, contact-type dermatitis has been reported in individuals with exposure to textiles coloured with dyes containing Disperse Yellow 3. The prevalence of contact dermatitis to the chemical in Australia is unknown. In addition, while consumer exposure is likely to be low, the associated cancer risks give cause for concern. A Tier III assessment is recommended to further characterise the exposure to the chemical and the hazards of the amine metabolites and the risks from the use of the chemicals in textile and paper products.

Occupational Risk Characterisation

During product formulation, exposure of workers to the chemical may occur, particularly where manual or open processes are used. These may include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. Worker exposure to the chemical at lower concentrations may also occur while using formulated products containing the chemical. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical systemic long-term health effects, the chemicals could pose an unreasonable risk to workers unless adequate control measures to minimise exposure are implemented. The chemicals should be appropriately classified and labelled to ensure that a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) has adequate information to determine the appropriate controls.

The *Guidance on the interpretation of workplace exposure standards for airborne contaminants* advises that 'exposure to carcinogens should be eliminated or minimised so far as is reasonably practicable' (Safe Work Australia, 2012).

The data available support an amendment to the hazard classification in the HSIS (refer to **Recommendation** section).

NICNAS Recommendation

Further risk management is required. Sufficient information is available to recommend that risks to public health and safety from the potential use of the chemicals in hair dyes and domestic products be managed through changes to poisons scheduling, and risks for workplace health and safety be managed through classification and labelling.

A Tier III assessment is recommended to further characterise the hazard, exposure and risks from the use of the chemical in textile and paper products.

Regulatory Control

Public Health

Appropriate scheduling and labelling should be undertaken to mitigate risk when the chemical is used in cosmetic products. Due to the toxicity profile, this chemical should be considered for listing in Schedule 6 of the *Standard for the uniform scheduling of medicines and poisons* (SUSMP). Matters to be taken into consideration include:

- the chemical has identified use in hair dye products;
- the chemical is a known sensitiser which has elicited positive reactions in patch tests at concentrations of 0.01 %;
- the chemical is carcinogenic in animals with evidence of a genotoxic mode of action; and
- the chemical is prohibited for use in cosmetics overseas.

Work Health and Safety

The chemical is recommended for classification and labelling under the current approved criteria and adopted GHS as below. This assessment does not consider classification of physical and environmental hazards.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Sensitisation	May cause sensitisation by skin contact (Xi; R43)*	May cause an allergic skin reaction - Cat. 1 (H317)
Genotoxicity	Muta. Cat 3 - Possible risk of irreversible effects (Xn; R68)	Suspected of causing genetic defects - Cat. 2 (H341)
Carcinogenicity	Carc. Cat 3 - Limited evidence of a carcinogenic effect (Xn; R40)*	Suspected of causing cancer - Cat. 2 (H351)

[a] Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)].

[b] Globally Harmonized System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third Edition.

* Existing Hazard Classification. No change recommended to this classification

Advice for industry

Control measures

Control measures to minimise the risk from oral, dermal, ocular and inhalation exposure to the chemicals should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate, or minimise risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemicals are used. Examples of control measures which could minimise the risk include, but are not limited to:

- using closed systems or isolating operations;
- using local exhaust ventilation to prevent the chemicals from entering the breathing zone of any worker;
- health monitoring for any worker who is at risk of exposure to the chemical[s], if valid techniques are available to monitor the effect on the worker's health;
- minimising manual processes and work tasks through automating processes;
- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemicals.

Guidance on managing risks from hazardous chemicals are provided in the *Managing risks of hazardous chemicals in the workplace—Code of practice* available on the Safe Work Australia website.

Personal protective equipment should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk. Guidance in selecting personal protective equipment can be obtained from Australian, Australian/New Zealand or other approved standards.

Obligations under workplace health and safety legislation

Information in this report should be taken into account to help meet obligations under workplace health and safety legislation as adopted by the relevant state or territory. This includes, but is not limited to:

- ensuring that hazardous chemicals are correctly classified and labelled;
- ensuring that (material) safety data sheets ((M)SDS) containing accurate information about the hazards (relating to both health hazards and physicochemical (physical) hazards) of the chemicals are prepared; and
- managing risks arising from storing, handling and using a hazardous chemical.

Your work health and safety regulator should be contacted for information on the work health and safety laws in your jurisdiction.

Information on how to prepare an (M)SDS and how to label containers of hazardous chemicals are provided in relevant codes of practice such as the *Preparation of safety data sheets for hazardous chemicals—Code of practice* and *Labelling of workplace hazardous chemicals—Code of practice*, respectively. These codes of practice are available from the Safe Work Australia website.

A review of the physical hazards of these chemicals has not been undertaken as part of this assessment.

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