ANSES Opinion
Request No. 2024-AUTO-0079

The Director General

Maisons-Alfort, 21 January 2025

OPINION
of the French Agency for Food, Environmental and Occupational Health & Safety

on the review of knowledge of the renal toxicity of glyoxylic acid in hair-straightening products

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It also contributes to the protection of the health and welfare of animals, the protection of plant health, the evaluation of the nutritional characteristics of food and the protection of the environment by assessing the impact of regulated products.
It provides the competent authorities with all necessary information concerning these risks as well as the requisite expertise and scientific and technical support for drafting legislative and statutory provisions and implementing risk management strategies (Article L.1313-1 of the French Public Health Code).
Its opinions are published on its website. This opinion is a translation of the original French version. In the event of any discrepancy or ambiguity the French language text dated 21 January 2025 shall prevail.

On 11 June 2024, ANSES issued an internal request to produce a review of knowledge of the renal toxicity of glyoxylic acid found in hair-straightening products.

1. BACKGROUND AND PURPOSE OF THE REQUEST

Since 1 January 2024, ANSES has been responsible for vigilance and expert appraisal relating to cosmetics and tattoo products, as well as the substances they contain.

On 6 January 2024, as part of the cosmetovigilance scheme it operates under Article L.5131-12 of the French Public Health Code, the Agency was notified of a case of acute kidney injury associated with a hair-straightening product containing glyoxylic acid.

In view of:

- the severity of the adverse effect described (recurrent acute kidney injury leading to several hospitalisations),

- the publication on this case by the nephrologists monitoring the patient, suggesting a causal link between this effect and glyoxylic acid,
- the existence of similar cases reported in Israel,

ANSES issued an internal request to produce a review of knowledge of the renal toxicity of glyoxylic acid found in hair-straightening products.

Since this first case, other cases of acute kidney injury following the application of hair-straightening products containing glyoxylic acid have been reported to ANSES and analysed.

On 6 June 2024, the French National Academy of Medicine published a press release on chemical hair straightening and health risks[1].

Hair-straightening products are cosmetic products as defined in Article 2 of Regulation (EC) No 1223/2009 on cosmetic products[2]. Article 3 of this Regulation stipulates that any “cosmetic product made available on the market shall be safe for human health when used under normal or reasonably foreseeable conditions of use". Before a cosmetic product can be placed on the market, therefore, the industry must ensure that its safety is assessed on the basis of appropriate information.

Within this EU regulatory framework, the European Commission can mandate its Scientific Committee on Consumer Safety (SCCS) to issue opinions on the safety of certain cosmetic substances. This request can arise from emerging safety concerns, and may lead to a substance being prohibited or its conditions of use restricted. While analysing the above reports, ANSES noted that glyoxylic acid had not been assessed by the SCCS and is not subject to any restrictions on use.

The aim of this expert appraisal is therefore to document the need to conduct a risk assessment at European level in order to guarantee consumer safety via the introduction of possible regulatory provisions, such as glyoxylic acid's inclusion in Annex II (prohibited substances) or Annex III (substances with restrictions on use) of the above-mentioned Regulation.

2. ORGANISATION OF THE EXPERT APPRAISAL

The expert appraisal was carried out in accordance with French standard NF X 50-110 "Quality in Expert Appraisals – General requirements of Competence for Expert Appraisals (May 2003)".

The issues being appraised lie within the scope of the Expert Committee on "Chemicals covered by the REACh and CLP Regulations" (CES REACh-CLP). The methodological and scientific aspects of the work were presented to the CES REACh-CLP on 15 October 2024. The work was adopted unanimously by this CES at its meeting on 3 December 2024.

[1] https://www.academie-medecine.fr/chemical-hair-straightening-and-health-risks/?lang=en

[2] A "cosmetic product" means any substance or mixture intended to be placed in contact with the external parts of the human body (epidermis, hair system, nails, lips and external genital organs) or with the teeth and the mucous membranes of the oral cavity with a view exclusively or mainly to cleaning them, perfuming them, changing their appearance, protecting them, keeping them in good condition or correcting body odours.

ANSES analyses interests declared by experts before they are appointed and throughout their work in order to prevent risks of conflicts of interest in relation to the points addressed in expert appraisals.

The experts' declarations of interests are made public via the website: https://dpi.sante.gouv.fr/.

Hearings were held with the doctors who reported the first case of acute kidney injury to ANSES. In addition, regarding the cases described in the publication by Bnaya et al. (2023) and the occurrence of similar cases, both the authors and the Israeli Ministry of Health were contacted by email and the latter provided further information.

3. ANALYSIS

As part of its cosmetovigilance scheme, ANSES received several reports of acute kidney injury (AKI), potentially associated with the application of hair-straightening products containing glyoxylic acid.

Hair straightening is a technique currently used in hairdressing. Besides the use of mechanical accessories (hairdryers and/or straightening irons), chemical methods have been developed in recent years to straighten hair for longer periods of up to several months (Barreto et al., 2021; Gavazzoni Dias et al., 2015). The "Brazilian" procedure uses a combination of keratin and chemicals to straighten hair semi-permanently. Until it was totally prohibited in cosmetic products in 2019 due to its carcinogenic properties, formaldehyde was one of the main chemicals used.

The search for alternatives then led to the use of carbonyl compounds such as glyoxylic acid (Boga et al., 2014; Hatsbach de Paula et al., 2022; Leite et al., 2017, 2018). When used in these products, glyoxylic acid levels are generally between 3 and 10% (Leite et al., 2017; Bnaya et al., 2023), although they can vary from 0.1 to over 25%. Furthermore, although this expert appraisal focuses on glyoxylic acid, ANSES notes that hair-straightening products may also contain other carbonyl derivatives, such as glyoxyloyl (carbo)cysteine, glyoxyloyl keratin amino acids, etc. (Bnaya et al., 2023, CosIng[3]).

The general (and not exhaustive) conditions of use found on various websites (for brands, patents and in the women's press) indicate that the straightening solution is applied to previously washed hair, strand by strand, for between 10 and 60 minutes. The companies marketing these products recommend avoiding contact with the scalp (an application distance of 0.5 to 1 cm is generally advocated). Excess product is removed without rinsing. The straightening process is completed by blow-drying the hair and then using a straightening iron at a temperature of around 200°C. Application of the product containing glyoxylic acid and/or one of its derivatives is generally preceded and/or followed by the application of other hair treatment products (shampoo to prepare the hair, mask). The technique can be carried out by a hairdresser in a salon or in the home, or directly by the consumer, as these products are commercially available.

[3] https://ec.europa.eu/growth/tools-databases/cosing/details/34158

3.1. Description of the first reported case

This case involved a 28-year-old woman with no prior medical history.

The patient, aged 25 at the time of the first episode, presented with three episodes of acute kidney injury (AKI), each following a hair-straightening treatment in a hair salon. The product used for the third episode was "Hanene Lissage Coiffure l'EQUILIBRE" containing 8% glyoxylic acid. The products used in the previous episodes were unknown.

The first episode in June 2020 was associated with vomiting, diarrhoea, fever and lower back pain. Medical examinations revealed an increase in serum creatinine levels to 228 µmol/L[4]. A renal scan showed symmetrical kidneys with a small non-obstructive stone. Urine analysis found no infection. The patient was hospitalised and given intravenous hydration. The AKI subsided after rehydration with Ringer's solution (normal serum creatinine levels 77 µmol/L).

In April 2021, she experienced a second episode with similar symptoms. Serum creatinine levels peaked at 208 µmol/L. Treatment consisted of self-medication with *per os* hydration at home.

The third episode occurred in July 2022 and was associated with nausea, vomiting, back pain and sweating, which appeared within an hour of the hair treatment. Investigations revealed an increase in serum creatinine levels to 172 µmol/L and an increase in CRP[5] to 15 mg/L. The scan did not reveal any renal obstruction. After intravenous rehydration with sodium chloride solution, serum creatinine levels decreased to 151 µmol/L (still above normal). Renal function improved, with serum creatinine levels returning to normal (69 µmol/L) at the follow-up visit in August 2022. No tests for crystalluria or kidney stones were performed.

The only event common to all three episodes of AKI was the application of a hair treatment on the day symptoms began. With all three episodes, the first symptoms were a burning sensation on the scalp for the duration of the application, followed by the appearance of scalp ulcers (with scabs) in this patient, who regularly suffered from dandruff. Bilateral lower back pain appeared within an hour of applying the hair treatment, with the pain peaking after three hours, followed by nausea and asthenia on the same day.

An underlying genetic lithiasis in the patient such as primary hyperoxaluria[6] (based on the medical history of her brother, who had active lithiasis) was ruled out by whole-exome sequencing analysis (Robert et al., 2024a). The brother's oxalate levels were normal.

3.2. Other reports received via the cosmetovigilance scheme

In August 2024, ANSES received two new reports of AKI following the application of hair-straightening products containing glyoxylic acid.

- The first case concerned a 38-year-old woman.

[4] In general, normal levels in women vary between 50 and 100 µmol/L
[5] C-reactive protein (CRP) is an inflammatory marker measured in the blood. Its level can rise in the event of infection. The level is considered "normal" when below the threshold of 6 mg/L.
[6] Increased urinary secretion of oxalic acid

On 9 July 2024, her hair was straightened at home by a hairdresser using the product "Ines Lissage Hairstylist Nano Spiruline 1 Anti-frizz Mask" containing 9% glyoxylic acid. The product also contains very low concentrations (0.00065%) of glycolic acid, which degrades to glyoxylic acid.

Four hours after the product was applied, she experienced the following symptoms: nausea, asthenia, anorexia, myalgia, headache and thirst. On 10 and 11 July 2024, she still had the same symptoms, which improved after taking paracetamol. A doctor she consulted on 11 July prescribed tests that revealed elevated serum creatinine levels of 117 µmol/L (compared with a baseline creatinine level of 58 µmol/L, measured in July 2023). An improvement was observed with hydration, calcium supplementation and an oxalate-free diet as recommended by the doctor, without the need for hospitalisation. The reported diagnosis was KDIGO 2 acute kidney injury (staged classification of acute kidney injury of undetermined cause, see Annex 4). On 15 July, an improvement in renal function was noted, with a reduction in serum creatinine levels to 93 µmol/L. On 17 July, the patient reported intermittent headaches. On 22 July, serum creatinine levels were normal at 88 µmol/L.

- The second case concerned a 42-year-old woman with no prior medical history.

According to the report received by ANSES, the hair-straightening treatment was carried out in a hair salon on 17 July 2024 using the product "Protéine Bio Organique Soie AmlaNano Liss Hair" containing 20% glyoxylic acid. However, during the investigation, in December 2024, the hair salon manager told the Directorate General for Competition Policy, Consumer Affairs and Fraud Control (DGCCRF) that the product used on the consumer was in fact "Vitta Gold Nanoplex Arginina Hair Smoothing Protein, Crème de Lissage" containing 12.5% glyoxylic acid.

A few hours after application of the hair-straightening treatment, the woman began to experience lower back pain. She went to the hospital emergency department with suspected renal colic. The computed tomography (CT) scan was normal. Biological tests revealed normal serum creatinine levels of 97 µmol/L and an increase in CRP to 9.3 mg/L.

On 19 July, as she was still suffering from symptoms (lower back pain, discomfort, nausea), her general practitioner sent her back to the hospital emergency department. Biological tests revealed elevated serum creatinine levels of 180 µmol/L and a CRP of 47.7 mg/L. She was admitted to hospital and received antibiotic treatment with ceftriaxone prophylaxis for 72 hours, and hydration.

On 24 July, five days later, she was discharged from hospital with her serum creatinine levels still above normal, at 122 µmol/L. On 31 July, the results showed a favourable progression with normal serum creatinine levels of 90 µmol/L. The diagnosis was AKI of unspecified cause.

- Lastly, it should be added that since October 2024, several cases of AKI (some of which identified oxalate crystals in the renal biopsy) following the application of hair-straightening products have been reported to ANSES. However, no information is currently available on the hair-straightening products used. Pending further information, these cases are still being investigated, and it has not yet been possible to determine their causality.

These include one case reported by a nephrologist in October 2024. The patient was a 28-year-old woman with no previous medical history. Severe AKI was diagnosed following a hair-

straightening procedure applied by a hairdresser. The patient went to the hospital emergency department with abdominal pain. A renal biopsy was performed, which revealed calcium oxalate deposits.

3.3. Causality

Concerning the first three cases described, for which the investigations were completed, and in accordance with the methodology in force for defining the causality of adverse effects due to cosmetic products (SUE Reporting Guidelines[7]), **ANSES concluded that causality was likely** in view of (i) a chronology deemed compatible between exposure and the onset of symptoms, (ii) symptomatology (type and location) suggestive of the use of the cosmetic product and (iii) the absence of re-exposure to the product[8] and of additional examinations (test for crystalluria or renal biopsy) (causality assessment table in Annex 5).

These three cases were forwarded by ANSES to the European Information and Communication System for Market Surveillance (ICSMS[9]), in accordance with Regulation (EC) No 1223/2009 on cosmetic products. This is the comprehensive communication platform for market surveillance on non-food products and for mutual recognition of goods. ICSMS is also an intelligence mechanism for the reliable exchange of information among authorities.

As the other cases are still being investigated, it has not been possible to determine their causality.

3.4. Uses of glyoxylic acid (CAS No 298-12-4, EC No 206-058-5)

Glyoxylic acid is a registered substance[10] under the REACh Regulation (Regulation (EC) No 1907/2006) concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals. Between 10,000 and 100,000 tonnes are manufactured in and/or imported into the European Economic Area every year[11].

According to the European Commission's CosIng database of cosmetic ingredients placed on the market in Europe, glyoxylic acid is a cosmetic ingredient with antistatic, buffering and hair waving or straightening functions.

This substance has not been assessed by the European Scientific Committee on Consumer Safety (SCCS) and is not subject to any specific provisions under the Cosmetics Regulation.

The literature search found nothing on the presence of glyoxylic acid in cosmetics other than hair-straightening products, although this cannot be completely excluded due to its functions as reported in the CosIng database.

[7] https://single-market-economy.ec.europa.eu/sectors/cosmetics/market-surveillance_en
[8] It should be noted that the first case described (28-year-old woman) mentions three episodes of AKI caused by three different products, although the composition of two of them was unknown
[9] https://webgate.ec.europa.eu/single-market-compliance-space/market-surveillance "likely" is the second level, coming after "very likely" on a 5-level scale
[10] Because this expert appraisal did not set out to conduct an in-depth analysis of the registration dossier, its completeness with regard to the requirements defined in the REACh Regulation was not verified.
[11] https://echa.europa.eu/substance-information/-/substanceinfo/100.005.508

The substance is also used in the industrial manufacture of cleaning products, as well as home furnishing products, due to its corrosion-inhibiting, pH-regulating and anti-scale properties. In this context, glyoxylic acid is used as an intermediate in the synthesis of other substances, as well as in the manufacture of products for tanning, dyeing or impregnating leather, and metal products (BAuA, 2017).

3.5. Review of knowledge of the renal toxicity of glyoxylic acid

The aim of this review is to reach a conclusion on the renal toxicity of glyoxylic acid based on the knowledge available in the scientific literature and by assessing the quality of the scientific evidence on the causal relationship between the use of this substance and the occurrence of the adverse effect.

This review of knowledge is based firstly on data from the literature, extracted according to the methodology set out in Annex 2, and secondly on the data presented in the regulatory dossier available under the REACh Regulation (ECHA, 2024a[12]).

3.5.1. Clinical cases reported in the literature

Other similar clinical cases were searched for in the scientific literature, both in France and abroad. The results of this search are set out below.

- In a retrospective study carried out in Israel, Bnaya et al. (2023) described 26 cases of severe AKI following the use of hair-straightening products. They occurred between 2019 and 2022 and were identified retrospectively from 14 medical centres.

The patients were aged between 13 and 58 years. They experienced clinical symptoms (abdominal pain, lower back pain, nausea, vomiting, etc.) during or within three hours of application of the product. Scalp rashes were also reported in 10 patients (38% of cases).

Renal biopsies were performed in seven patients. Six showed deposits of calcium oxalate crystals, and one showed microcalcifications in the tubular cells, confirming the diagnosis of acute oxalate nephropathy as the main cause of the AKI. Renal function spontaneously returned to normal in all patients where the outcome was known.

For all the patients, the causality between exposure to the hair-straightening product and the onset of AKI was deemed probable by the authors. Eleven patients were exposed to keratin-based hair-straightening products containing "glycolic acid derivatives". By glycolic acid derivatives, the authors are referring to glyoxylic acid, glyoxyloyl carbocysteine and glyoxyloyl keratin amino acids. For the other patients, the type of hair-straightening product used was unknown. The authors nevertheless point out that the majority of hair-straightening products available on the Israeli market contain glycolic acid derivatives. An analysis by the Israeli Ministry of Health found glyoxylic acid levels of between 0.56 and 17.9% in this type of product. In one of the clinical cases, the composition of the product was known and did not contain glyoxylic acid but glyoxyloyl carbocysteine (Greenberg et al., 2022 included in Bnaya et al., 2023). This shows that the AKI may not have been caused solely by glyoxylic acid, but also by other related substances sharing comparable physico-chemical characteristics. In the specific

[12] https://echa.europa.eu/information-on-chemicals/registered-substances/-/disreg/substance/100.005.508

case of glyoxyloyl carbocysteine, this substance can potentially produce glyoxylic acid by hydrolysis. This reaction is promoted in aqueous and acidic environments and by high temperatures, three conditions that are met when the "Brazilian" procedure is carried out.

ANSES contacted the Israeli Ministry of Health as part of this expert appraisal, because following the above-mentioned publication, in 2022, the Ministry introduced a national ban on hair-straightening products containing glyoxylic acid, but not those containing derivatives. According to the Ministry, “The rationale was that there is increased absorption of glyoxylic acid via the scalp during use of hair straightening products, perhaps due to low pH of the products or form of use (heating).”

During these exchanges, the Ministry also stated that 14 new cases of AKI had been identified in the country between September 2022 and September 2024[13]. The patients, whose kidney injury was confirmed by creatinine measurement, were aged between 15 and 37 years. No information was available on whether or not biopsies had been performed. The products incriminated in these new cases, where these were known and/or laboratory tests had been carried out, had glyoxylic acid levels of up to 25.35% and acid pH values (below 1).

- In 2024 in Switzerland, Huber et al. (2024) reported a case of AKI in a 42-year-old woman following the application of a hair-straightening product. Renal biopsy revealed numerous calcium oxalate deposits, similar to the cases previously described in which a biopsy had been performed. However, no information was available about the product used, so the presence of glyoxylic acid in its composition could not be formally confirmed. In this clinical case, in view of the 24-hour urinary metabolic profile and the shape of the oxalate crystals observed in the biopsy, the authors ruled out a dietary origin or sustained hyperoxaluria.

- Lastly, a 2019 publication reported two cases of AKI in Egypt, in girls aged 10 and 17 years, respectively, following the use of formaldehyde-free hair-straightening products (Ahmed et al., 2019). However, the aim of this publication was not to discuss the possible role of glyoxylic acid in the occurrence of these reactions, as it focused on the potential role of formaldehyde. Physical examination revealed erosion of the scalp. Renal biopsies were performed in both cases, although the results were not reported by the authors. Nor did they provide the full composition of the products in question, and the ingredients mentioned in the publication do not contain either glyoxylic acid or its derivatives.

A table outlining all the identified cases is provided in Annex 3. In summary, 46 cases of AKI following the application of hair-straightening products were identified in the literature or via the cosmetovigilance scheme[14]. The composition of the products was rarely reported. However, as mentioned above, according to several authors, formaldehyde-free products used in the "Brazilian" procedure commonly contain glyoxylic acid (Bnaya et al., 2023, Boga et al., 2014).

[13] Ministry of Health, Israel, email correspondence, 30 October 2024
[14] Concerning the cases from the cosmetovigilance scheme in France: only those for which causality had been confirmed at the date of this opinion have been considered

3.5.2. Toxicokinetic data

No experimental studies have explored the absorption, distribution, metabolism or elimination (ADME) properties for glyoxylic acid.

However, in the absence of such studies, the dermal absorption capacity can be estimated by considering certain physico-chemical properties of the substance, such as (ECHA, 2024b):

- **molecular weight**: a molecular weight of less than 100 g/mol promotes dermal absorption.
- **solubility in water and log P (or log Kow)[15]:** for solubility values greater than 10,000 mg/L and a log P (or log Kow) of less than 0, the substance may be too hydrophilic to pass through the stratum corneum[16].

The molecular weight of glyoxylic acid (74.04 g/mol) therefore favours dermal absorption, in contrast to its solubility in water (1000 g/L) and its log P (-0.07 for the hydrated form).

The metabolism of glyoxylic acid has mainly been investigated in studies related to hyperoxaluria. Glyoxylic acid (or glyoxylate) is an endogenous substance involved in numerous enzymatic reactions. It can be generated from numerous precursors in different cellular compartments, including mitochondria, peroxisomes and the cytosol (Garelfs et al., 2024).

The different metabolic pathways are shown in Figure 1.

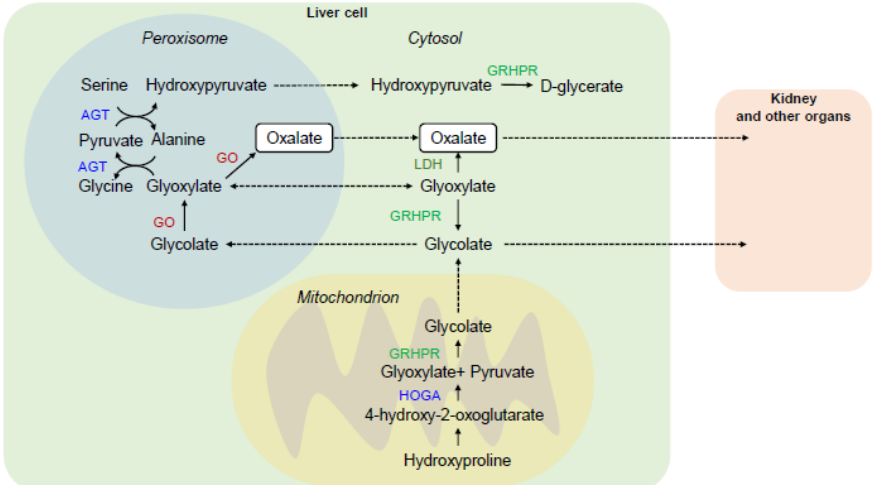

Figure 1: Simplified illustration of glyoxylate (or glyoxylic acid) metabolism in humans (Demoulin et al., 2022)

AGT: alanine-glyoxylate aminotransferase; GO: glycolate oxidase; GRHPR: glyoxylate reductase/hydroxypyruvate reductase; HOGA: 4-hydroxy-2-oxoglutarate aldolase.

Under physiological conditions, the main metabolic pathways for this substance are its conversion to glycolate by glyoxylate reductase (GRHPR) or to glycine by alanine-glyoxylate aminotransferase (AGT). These two enzymes are necessary to prevent the formation of

[15] n-octanol/water partition coefficient

[16] Latin for "horny layer": outermost layer of the epidermis made up of flattened, dried, completely keratinised anucleate keratinocytes, which then lose their cohesion and are shed (based on the definition in the French National Academy of Medicine's Medical Dictionary https://www.academie-medecine.fr/le-dictionnaire/index.php?q=stratum corneum#:~:text=Ensemble des couches les plus,selon les zones du tégument.).

oxalate from glyoxylate, because conversion to oxalate – which can occur particularly when there is an excess of glyoxylic acid – is under the control of either peroxisomal glycolate oxidase (GO) or cytoplasmatic lactate dehydrogenase (LDH) (Schnedler et al., 2011, Demoulin et al., 2021). The liver is responsible for 60-80% of plasma oxalate synthesis. However, this reaction can occur in most tissues, including the kidneys, as LDH is found in the majority of tissues and organs (Gibbs et al., 1977; Behnam et al., 2006). The main route of oxalate excretion is the kidney, where it is eliminated via glomerular filtration and tubular secretion.

In the event of an excess of glyoxylic acid and/or an enzymatic inability to counter the formation of oxalate, **it will accumulate in the body**. **In the kidney, in the presence of calcium, oxalate will precipitate in the parenchyma in the form of calcium oxalate crystals**, which have very low solubility in urine. **This accumulation can lead to impaired renal function** (Demoulin et al., 2022).

3.5.3. Toxicity data in animals

The identification and analysis of data for this expert appraisal focused mainly on the renal toxicity of glyoxylic acid.

3.5.3.1. Data on local toxicity

The ability of glyoxylic acid to induce skin sensitisation was demonstrated in particular in a local lymph node stimulation assay carried out in 2008 in accordance with OECD[17] Test Guideline 429. This study was conducted in Balb/c rats exposed to glyoxylic acid diluted 50% in acetone, at concentrations ranging from 1.25 to 40%. Skin irritation was observed at the highest concentration. The EC3 value, the estimated concentration inducing lymphocyte proliferation three times higher than the negative control, was 5.05% (i.e. above the 2% threshold for classification) (ECHA 2018 & 2024a[12]). The substance therefore has the following harmonised classification: Skin sensitisation, Category 1B (H317), "may cause an allergic skin reaction" according to the CLP Regulation (EC) No 1272/2008 on classification, labelling and packaging of chemicals and mixtures.

According to a skin irritation study carried out in 1984 on six male New Zealand rabbits, in accordance with OECD Test Guideline 404, the application of 0.5 mL of glyoxylic acid (diluted 50% in an aqueous solution) for 4 hours did not induce irritation, apart from a very slight erythema (barely perceptible) in one animal (ECHA, 2018 & 2024a[12]).

Lastly, according to the current harmonised classification of the substance, it causes serious eye damage (Eye Dam.1 – H318).

[17] Organisation for Economic Co-operation and Development

3.5.3.1. Data on systemic toxicity

- Dermal route data

In a study carried out on Sprague Dawley rats in 2004 in accordance with OECD Test Guideline 402, skin application of glyoxylic acid (diluted 50% in an aqueous solution) at a dose of 2000 mg/kg bw for 24 hours did not produce any abnormalities on macroscopic examination (it was not specified whether the kidneys were investigated). No microscopic analysis was reported (ECHA, 2024a[12]).

The nephrologists who reported the first clinical case (described in Section 3.1.1 of this opinion) conducted a toxicity study on rodents in order to investigate the role of the hair-straightening cream used, and more specifically the glyoxylic acid, in the onset of AKI (Robert et al., 2024a and b). Four groups of female C57BL/6J mice were exposed as follows:

- hair-straightening product used by the patient, i.e. "Hanene Lissage Coiffure l'EQUILIBRE",
- petroleum jelly containing 10% glyoxylic acid,
- petroleum jelly containing 10% glycolic acid (the product in question does not contain glycolic acid. However, the authors included this group in view of the fact that this substance is found in many cosmetics and given its metabolism, it could also induce oxalate formation in the liver),
- petroleum jelly without any active compound (control).

One gram of product was applied to the upper back twice, 6 hours apart. To achieve uniform application, a 3-minute skin massage was performed under brief isoflurane-induced anaesthesia. The animals were isolated to avoid potential ingestion of the product by fellow animals. The animals were sacrificed 28 hours after the first application.

Two experiments were carried out: the first, with five mice per group, consisted in analysing renal function and the second, with six mice per group, consisted in assessing glycolate, oxalate and creatinine excretion.

In the groups exposed to the hair-straightening product and the cream containing 10% glyoxylic acid, the authors observed the following, compared with the control group:

- a statistically significant increase in oxalate and glycolate in urine,
- the presence of calcium oxalate monohydrate crystals in urine, some of which had a shape similar to that described in cases of ethylene glycol poisoning,
- a statistically significant increase in plasma creatinine and urea levels,
- tubular necrosis and calcium oxalate crystal deposits in the kidneys,
- moderate reddening of the skin in some mice.

These observations are comparable to those observed in the clinical cases described in Sections 3.1 and 3.2.

On the other hand, in the group exposed to the glycolic acid cream, the results were normal apart from a slight, albeit statistically significant, increase in urinary oxalate and glycolate

excretion. The authors put forward several hypotheses to explain the differences between the groups exposed to glyoxylic or glycolic acid, both of which metabolise to oxalate:

- a difference in dermal absorption between these two substances. However, ANSES notes that this has not yet been documented for either of these substances,
- the fact that glycolic acid must first be metabolised to glyoxylic acid before forming oxalate, whereas glyoxylic acid is metabolised directly to oxalate by LDH (Figure 1). This hypothesis would suggest that a higher quantity of glycolic acid is needed for the renal effects to occur.

On the basis of this study, the authors concluded that these results provide evidence of a causal link between glyoxylic acid and the development of nephropathy induced by calcium oxalate deposits following the application of hair-straightening products containing it.

No repeated dermal toxicity studies are available for the substance, either in the literature or in the registration dossier available on the ECHA website.

- Oral route data

An acute toxicity study in Wistar rats at doses of between 1250 and 5000 mg/kg bw/d of glyoxylic acid (diluted 50% in an aqueous solution) was carried out in 1975. The lethal dose inducing 50% mortality was calculated at 2528 mg/kg bw/d. The dead animals had pale intestines at necropsy. No abnormalities were reported in live animals, but it was not specified whether the kidneys had been investigated (ECHA, 2024a[12]).

Only one repeated toxicity study with glyoxylic acid is available.

This was a combined repeated-dose toxicity study with the reproduction/developmental toxicity screening test conducted in 2005 according to OECD Test Guideline 422. In this study, glyoxylic acid (diluted 50% in an aqueous solution) was administered to Crj:CD (SD) rats in feed for around 5 weeks[18], at doses of 0, 1000, 6000 or 18,000 ppm (i.e. around 70, 200 and 600 mg/kg/d respectively in males and 80, 240 and 730 mg/kg/d in females).

According to the summary available on the ECHA website, no kidney effects were reported. However, no urine analysis was performed and it was not specified whether a histopathological analysis of the kidneys was carried out. A NOAEL[19] of 6000 ppm (i.e. 200 mg/kg bw/d) was proposed by the industry on the basis of a statistically significant reduction in body weight gain observed in males.

Lastly, it should be noted that in order to fulfil its obligations with regard to the information requirements set out in the REACh Regulation concerning data on repeated toxicity, the industry also proposes a read-across approach with glyoxal in its registration dossier. No kidney effects have been reported with this substance.

[18] Exposure for 14 days prior to mating, during mating and gestation and up to day 4 of lactation
[19] No observed adverse effect level – Highest dose at which no toxic or adverse effect is observed.

3.5.4. Additional evidence

3.5.4.1. Mechanistic data from the scientific literature

In order to understand the cellular mechanisms leading to the formation of oxalate crystals and/or to identify compounds that could limit their formation, numerous publications have sought to develop experimental models of nephropathy induced by oxalate deposits. Some of the available models involve intraperitoneal injection of glyoxylic acid for several days (between 5 and 15 days), mainly in mice. Doses are generally between 60 and 100 mg/kg bw/d. According to some authors, glyoxylic acid may be one of the most effective oxalate precursors for inducing oxalate deposit nephropathy among those tested (Okada et al., 2007; Oh et al., 2011). These studies confirm that systemic exposure to glyoxylic acid (here via repeated intraperitoneal injection) induces the formation of oxalate crystals in rodents and the kidney lesions associated with their presence (Ming et al., 2022; Ding et al., 2021).

3.5.4.2. Analogy with the nephrotoxicity of ethylene glycol

Ethylene glycol is a substance known to induce oxalate crystal deposit nephropathy following exposure in humans, particularly in cases of poisoning, as well as in rodents (Fowles et al., 2017, Environment Canada & Health Canada, 2000). Glyoxylic acid is one of the intermediate metabolites in the breakdown of ethylene glycol to oxalic acid (Figure 2). This evidence may therefore also support the role of glyoxylic acid in the AKIs observed following the "Brazilian" procedure, since it has the same effect.

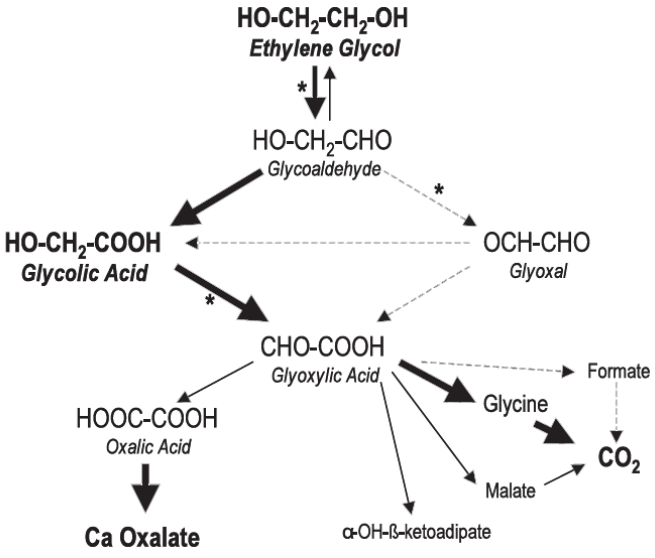

Figure 2: Metabolism of ethylene glycol (Corley et al., 2011)[20]

[20] Steps in the metabolism of ethylene glycol considered to be slow are indicated with an "*", while the main pathways leading to known excretion products are indicated with bold arrows. Pathways where there is a doubt about their contribution to in vitro metabolism are indicated with dotted arrows.

3.5.4.3. Factors promoting oxalate-induced AKIs

3.5.4.3.1. Hyperoxaluria

There are two kinds of nephropathy-inducing hyperoxaluria: so-called "primary" and "secondary".

- Primary hyperoxaluria

This type of hyperoxaluria results from deficiencies in liver enzymes such as AGT and GRHPR (Salido et al., 2012; Garrelfs et al., 2024). These enzymatic pathways, which are involved in the metabolism of glyoxylic acid, protect the body against the accumulation of oxalate.

Primary hyperoxaluria type 1, which results from a genetic deficiency of functional AGT, is the most severe form and the one found in the vast majority of patients (70-80%). However, it remains a rare disease, with a prevalence of 1 to 3 cases per 1 million people (Bao et al., 2023).

Among the cases identified in this expert appraisal, it was clearly mentioned that a genetic disorder linked to oxalate metabolism had been ruled out by exome analysis in the case of the patient monitored and described by Robert et al. (2024). For the other cases, no such disease was reported in the description of the medical history.

- Secondary hyperoxaluria

This type of hyperoxaluria is more frequent than primary hyperoxaluria and may be associated with various known causes, such as in (Bao et al., 2023; Demoulin et al., 2022):

- increased dietary intake of oxalate or oxalate precursors, as around 20 to 40% of the oxalate in plasma comes from the diet. Food sources primarily include spinach, rhubarb, chaga mushrooms, black tea, nuts (peanuts, cashews and almonds) and star fruit. Ascorbic acid (vitamin C) is an oxalate precursor;
- increased intestinal absorption of oxalate: fat malabsorption due to various causes (pancreatic disorders, Roux-en-Y gastric bypass surgery performed to treat obesity, short bowel syndrome, Crohn's disease, use of a gastrointestinal lipase inhibitor (orlistat)) leads to steatorrhea, calcium binding by fatty acids in the intestinal lumen, increased intestinal absorption of free oxalate, and higher ileal and colonic permeability to oxalate. Exocrine pancreatic insufficiency, characterised by a deficit in the production of pancreatic enzymes, can also lead to poor digestion of food, manifested clinically by steatorrhea;
- a reduction in the intestinal breakdown of oxalate by bacteria, for example when taking antibiotics or in situations of obesity;
- other factors such as dehydration, use of diuretics or inflammation can increase urinary oxalate concentrations. It has also been noted that plasma concentrations of glyoxylic acid are higher in people with diabetes;
- chemical poisoning (e.g. ethylene glycol).

On the first point, only Huber et al. (2024) clearly ruled out a dietary origin in the onset of AKI. This information was not mentioned in the other cases. Regarding the other factors, no such diseases or conditions were mentioned in the patients' histories, even though they are potentially aggravating factors.

3.5.4.3.2. Factors promoting systemic exposure to glyoxylic acid

As previously stated, no data on the dermal absorption of glyoxylic acid were found in the literature.

However, many extrinsic factors influence the dermal absorption of substances found in the environment, including (WHO, 2006; EFSA, 2017):

- **exposure site**: dermal absorption is greater in areas of the body where the skin is thin and/or there is a lot of hair;
- **skin condition**: dermal absorption is greater if skin is damaged or irritated;
- **skin temperature and hydration**: these two parameters are linked and influence dermal absorption. In particular, a rise in temperature increases absorption by promoting perspiration (and therefore hydration) and by increasing blood flow in the hypodermis (conversely, a drop in temperature will induce vasoconstriction, which will reduce dermal absorption). Occlusion (wearing gloves, skin folds, etc.) also increases skin hydration and promotes dermal absorption;
- **environment**: the parameters of the medium (physical state, pH, etc.) in which the substance is found influence dermal absorption (for example, the lower the pH, the greater the absorption).

Lastly, **the duration, frequency, concentration and surface area of exposure** influence the quantity absorbed.

Once these various factors are known, a number of points can be made about exposure to glyoxylic acid:

- Concerning the "**skin condition**", this factor is particularly affected by the irritating and sensitising nature of the ingredients/products applied. If a substance is a skin irritant or corrosive, damage to the skin will promote dermal absorption. Similarly, if a substance is identified as a skin sensitiser, this suggests that a certain amount of absorption must take place (ECHA, 2024b).
    - Glyoxylic acid has a harmonised classification under the CLP Regulation as a substance that causes serious eye damage (Eye Dam.1 – H318) and as a skin sensitiser (Skin Sens. 1B – H317).
    - Hair-straightening products may generally be associated with various adverse effects on the scalp and hair: desquamation, burns, inflammation of the scalp, eczema, hair damage and hair loss (Hatsbach de Paula, 2022).
    - Similar effects were reported in the specific case of the hair-straightening products referred to in this expert appraisal:
        - when information on the condition of the scalp was documented in the clinical cases listed, several patients who developed AKI had local irritation;
        - skin reddening was also observed in experimental studies in mice exposed to glyoxylic acid (Anderson, 2008; Robert et al., 2024).

- Concerning the "**exposure site**":
  - absorption through the scalp is probably higher than in most other areas of the skin surface, due to the abundance of hair follicles.

- Concerning the "**temperature and hydration**" factor:
  - the straightening product is applied to wet hair. The procedure then involves two phases of heating the hair – with a hairdryer and then a straightening iron at around 200°C – after applying the straightening product. As well as providing more favourable conditions for absorption, heating can damage the hair's coating and the scalp. Moreover, using a straightening iron is often accompanied by the emission of fumes potentially containing chemicals that can then be inhaled.

- Concerning the "**exposure time**":
  - according to the hair-straightening procedure, the product is applied for 10 to 60 minutes and the hair is not rinsed afterwards.

- Concerning the "**medium**" factor:
  - as previously mentioned, hair-straightening products containing glyoxylic acid have acidic pH values (below 4, and more generally between 1 and 3). Bnaya et al. (2023) also reported pH values below 1 for certain products. This acidic pH could also, in itself, promote irritation of the scalp.

In summary, these different points demonstrate the favourable conditions for dermal absorption of glyoxylic acid offered by the hair-straightening procedure.

3.5.4.4. Alternative hypothesis: the case of formaldehyde

An alternative hypothesis put forward in some publications is that AKI could be caused, at least in part, by exposure to formaldehyde during the application of hair-straightening products (Bnaya et al., 2023; Abu-Amer et al., 2022).

As mentioned above, formaldehyde is prohibited as a cosmetic ingredient in Europe (Annex II of the Cosmetics Regulation). However, levels of formaldehyde have been detected in some hair-straightening products claiming to be "formaldehyde-free" (Maneli et al., 2014; Ahmed et al., 2019; Bnaya et al., 2023; FDA[21]). For example, Maneli et al. (2014) reported formaldehyde levels of between 0.96 and 1.4% in six out of seven keratin-based products used for the "Brazilian" procedure, analysed in South Africa in 2012.

Furthermore, because of its chemical structure (presence of an aldehyde group), glyoxylic acid can potentially release formaldehyde when subjected to high temperatures, as is the case with keratin-based hair straightening. Lastly, formaldehyde has been found in air measurements in beauty salons, despite formaldehyde-free products being used (Peteffi et al., 2016).

The renal toxicity of formaldehyde has rarely been substantiated in the literature. Some authors have nevertheless reported that formaldehyde inhalation in rats may be responsible for kidney damage associated with inflammation and oxidative stress (Kum et al., 2007; Zararsiz et al., 2007; Ramos et al., 2017). However, in the present case, biopsies taken from certain patients and microscopic examinations of mice treated with a glyoxylic acid-based product **showed**

[21] https://www.health.ny.gov/environmental/chemicals/formaldehyde/docs/consumer.pdf

deposits of calcium oxalate crystals in the kidneys. In the current state of knowledge, therefore, these observations do not support formaldehyde as the causal agent of the AKI observed following the "Brazilian" procedure (Bnaya et al., 2023; Robert et al., 2024b).

3.6. Analysis and conclusions of the CES

While conducting this expert appraisal, and as part of its cosmetovigilance scheme, ANSES finalised the causality assessment (which began at the start of the year) of three reports of serious adverse effects – in this case AKI – following the application of hair-straightening products containing glyoxylic acid. The severity of the effects led to two of the three patients being admitted to hospital. The outcome was favourable in all cases following hydration treatment. Causality was determined as "likely" for each of these reports. Other reports of adverse effects following the use of hair-straightening products have since been received but are still being investigated.

After investigation, some cases were also reported in the literature following observations in other countries, bringing the number of identified cases to 46[22]. They concerned women aged between 13 and 58 years, with no prior medical history, presenting with relatively non-specific clinical symptoms such as nausea, vomiting and pain, sometimes accompanied by a scalp rash. Acute kidney injury was confirmed by a measured increase in serum creatinine levels. A renal biopsy was carried out for some cases and showed calcium oxalate deposits. In most cases, the composition of the product used was not known. However, where data were available, glyoxylic acid or glyoxylic acid derivatives were found in the product. These substances are found widely in keratin-based hair-straightening products on the market.

Regarding:

- the symptomatology in the clinical cases;
- the chronology (symptoms appeared very quickly during or after application of the hair-straightening product);
- the recurrent nature of the AKI observed in the first French case after each hair-straightening procedure;
- the composition of the hair-straightening products, which can contain glyoxylic acid at levels of up to 25%;
- the metabolism of this substance and the pathophysiological mechanism associated with the hyperoxaluria;
- the renal toxicity data available on the substance and on substances that degrade into glyoxylic acid (e.g. ethylene glycol);

the role of glyoxylic acid in triggering the AKI is considered to be highly probable. In addition, the product's formulation and the conditions associated with the hair-straightening procedure are important parameters to be taken into account in the occurrence of this adverse effect. The acidic pH and the irritant or even corrosive nature of these products, combined with factors such as the application site, temperature and duration of exposure, are all conditions favouring the dermal absorption of glyoxylic acid.

[22] For the cases from the cosmetovigilance scheme in France: only those for which causality had been confirmed at the date of this opinion have been considered

To date, this substance has not been subject to any specific provisions under the Cosmetics Regulation (and particularly its Annexes II and III[23]), and its use is therefore neither regulated nor restricted. The process for prohibiting or restricting the use of a substance in cosmetic products is carried out at European, not national, level, as the safeguard clause applies to cosmetic products and not to substances (Article 27 of the Cosmetics Regulation[24]). In the event of any human health concerns, the European Commission can mandate its Scientific Committee on Consumer Safety (SCCS) to issue opinions on the safety of certain cosmetic substances. On the basis of these opinions, the Commission can then amend the annexes to the Cosmetics Regulation. **In this context, the CES recommends that a risk assessment be conducted by the SCCS to limit or even prohibit the use of this substance in hair care products. Other potentially affected products should also be identified.**

Pending this risk assessment and its conclusions, the CES recommends not using hair-straightening products containing glyoxylic acid. The CES notes that these products' instructions and conditions of use do not guarantee consumer safety with regard to the renal toxicity of glyoxylic acid.

The CES also recommends paying particular attention to exposure to hair-straightening products containing substances that can break down into glyoxylic acid. These may include carbonyl derivatives, such as glyoxyloyl (carbo)cysteine, glyoxyloyl keratin amino acids, etc.

Lastly, the CES would like to draw attention to the fact that these products can potentially release formaldehyde, a carcinogenic substance, when the hair is heated.

4. AGENCY CONCLUSIONS AND RECOMMENDATIONS

The French Agency for Food, Environmental and Occupational Health & Safety issued an internal request to carry out a targeted review of knowledge of the renal toxicity of glyoxylic acid after analysing an initial report to the cosmetovigilance scheme of a case of AKI following the application of hair-straightening products containing this substance. This decision was based on the results of an analysis of the case[25], as well as the existence of similar cases reported abroad and a publication suggesting a causal link between this effect and the glyoxylic acid provided by the product.

Glyoxylic acid is a substance that occurs naturally in the body, but can also come from various exogenous sources (dietary intake in particular). Under physiological conditions, elimination mechanisms regulate its level. However, in specific situations (excessive dietary intake, particular diseases, exposure to chemical products, etc.) these mechanisms may be insufficient, leading to an accumulation of oxalate crystals that can impair renal function.

ANSES endorses the conclusions of the CES REACh-CLP: all the information analysed to date, i.e. the cases and the scientific literature, leads to the finding that the causal role of glyoxylic acid is considered highly probable in triggering acute kidney injury. ANSES also

[23] Annex II: prohibited substances; Annex III: substances subject to restrictions

[24] Article 27: Safeguard clause: *In the case of **products** meeting the requirements listed in Article 25(1), where a competent authority ascertains, or has reasonable grounds for concern, that a cosmetic product or products made available on the market present or could present a serious risk to human health, it shall take all appropriate provisional measures in order to ensure that the product or products concerned are withdrawn, recalled or their availability is otherwise restricted [...]*.

[25] The adverse effect was rated as "severe" and the level of causality established as "likely"

endorses the recommendations made by the CES REACh-CLP, and in particular the following points:

Firstly, ANSES **recommends that a risk assessment be conducted to determine whether the use of this substance in hair care products should be restricted or even prohibited under the Cosmetics Regulation** (EC) No 1223/2009. To do this, ANSES recommends that the competent French authorities present this need for assessment, along with the health concerns clearly identified in this opinion, at European level, which in practice should lead to the European Commission mandating the SCCS to evaluate the substance.

ANSES underlines the need for the assessment body to have access to reliable and relevant toxicological data. In the current expert appraisal, the animal data supported the causal role of glyoxylic acid in the effects observed in humans. ANSES also advocates that the recommended risk assessment examine more broadly the issue of cosmetic substances (found in hair products and other cosmetic products) that can be metabolised into glyoxylic acid or oxalate, thereby contributing to consumer overexposure (glyoxyloyl (carbo)cysteine, glyoxyloyl keratin amino acids, glyoxal, oxalate salts, etc.).

Secondly, pending the results of this European assessment, ANSES **stresses and reiterates the experts' recommendation not to use hair-straightening products containing glyoxylic acid**. It points out that it already made this recommendation, in light of the analysis of the cosmetovigilance cases, jointly with the Directorate General for Health and the Directorate General for Competition, Consumer Affairs and Fraud Control, on 16 October 2024[26]. This press release reinforces the one by the French National Academy of Medicine dated 6 June 2024 on the risks associated with the use of hair-straightening products containing glyoxylic acid.

ANSES also stresses that while these communications have led to the reporting of new cases, given the demonstration of a possible link between AKI and the "Brazilian" procedure, the number of cases identified is likely to be underestimated. In the event of symptoms such as abdominal or lower back pain, nausea and/or vomiting occurring in the hours following (or even during) exposure to a product containing glyoxylic acid, it therefore strongly advises consulting a doctor promptly or calling a poison control centre, mentioning the use of a hair-straightening product. This recommendation applies to both users and hairdressing professionals carrying out hair-straightening procedures. Although none of the reported cases have so far involved these professionals, increased vigilance is required in the event of these symptoms occurring in the workplace.

In addition, ANSES points out that it is the responsibility of the companies placing these products on the market to ensure that the cosmetics they design and market are safe for human health. While the cosmetovigilance work carried out did not lead to any particular product being identified, neither did it conclude that the application recommendations were adequate for avoiding any risk situation. Therefore, again without waiting for the findings of the European assessment work and the continued analysis of the reports received, the Agency recommends that companies marketing cosmetic products containing glyoxylic acid re-examine the relevance of their demonstration of product safety (Article 10 of the Cosmetics Regulation) and the adequacy of the precautions for use contributing to safe use of the products.

[26] https://www.anses.fr/fr/system/files/press-2024-08.pdf

Lastly, as part of the European Union's Chemicals Strategy for Sustainability, which aims to better protect human health and the environment, a targeted revision of the Cosmetics Regulation was planned for 2022[27]. To date, this revision has not been completed. On the other hand, the European Commission[28] is preparing a full evaluation of the Cosmetics Regulation, aimed mainly at assessing its relevance in terms of its objectives, which are to 1) protect consumer health by ensuring that all cosmetics meet strict safety requirements before being placed on the market, and 2) ensure the functioning of the internal market for cosmetic products. In view of this expert appraisal and the vigilance work that preceded it, ANSES believes that the example of glyoxylic acid calls for the current regulatory provisions to be supplemented, particularly in the event of health concerns about any substance used in different cosmetic products, in order to facilitate and accelerate the European assessment when a risk assessment dossier is submitted by a Member State to the SCCS or any body succeeding it.

Pr Benoit VALLET

27 https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/13197-EU-chemicals-strategy-for-sustainability-Cosmetic-Products-Regulation-revision-_en

28 https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/14433-Cosmetic-Products-Regulation-evaluation_en

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Cosmétiques, acide glyoxylique, produit lissant capillaire, insuffisance rénale aiguë

Cosmetics, glyoxylic acid, hair straightening product, acute kidney injury

REFERENCES

Abu-Amer, Nabil, Natalie Silberstein, Margarita Kunin, Sharon Mini, and Pazit Beckerman. 2022. "Acute Kidney Injury Following Exposure to Formaldehyde-Free Hair-Straightening Products". *Case Reports in Nephrology and Dialysis* 12(2): 112-16. https://doi.org/10.1159/000525567.

Ahmed, Heba Mostafa, Shimaa Hassan El-Attat, and Wesam Ismail. 2019. "Acute Kidney Injury Following Usage of Formaldehyde-Free Hair Straightening Products". *Iranian Journal of Kidney Disease* 13(2):129-131. PMID: 30988250.

Anderson, Stacey E., Jason E. Ham, and Albert E. Munson. 2008. "Irritancy and Sensitization Potential of Glyoxylic Acid". *Journal of Immunotoxicology* 5(2): 93-98. https://doi.org/10.1080/15476910802085681.

Bao, Daorina, Yu Wang, and Ming-hui Zhao. 2023. "Oxalate Nephropathy and the Mechanism of Oxalate-Induced Kidney Injury". *Kidney Diseases* 9(6): 459-68. https://doi.org/10.1159/000533295.

Barreto, Taynara, Flavia Weffort, Simone Frattini, Giselle Pinto, Patricia Damasco, and Daniel Melo. 2021. "Straight to the Point: What Do We Know So Far on Hair Straightening?" *Skin Appendage Disorders* 7(4): 265-71. https://doi.org/10.1159/000514367.

BAuA. 2017. CLH report. Proposal for harmonised classification and labelling. Glyoxylic acid…%.

Behnam, Joseph T., Emma L. Williams, Susanne Brink, Gill Rumsby, and Christopher J. Danpure. 2006. "Reconstruction of Human Hepatocyte Glyoxylate Metabolic Pathways in Stably Transformed Chinese-Hamster Ovary Cells". *Biochemical Journal* 394(2): 409-16. https://doi.org/10.1042/BJ20051397.

Bnaya, Alon, Nabil Abu-Amer, Pazit Beckerman, Alexander Volkov, Keren Cohen-Hagai, Meidad Greenberg, Sydney Ben-chetrit, et al. 2023. "Acute Kidney Injury and Hair-Straightening Products: A Case Series". *American Journal of Kidney Diseases* 82(1): 43-52.e1. https://doi.org/10.1053/j.ajkd.2022.11.016.

Boga, C., P. Taddei, G. Micheletti, F. Ascari, B. Ballarin, M. Morigi, and S. Galli. 2014. "Formaldehyde Replacement with Glyoxylic Acid in Semipermanent Hair Straightening: A New and Multidisciplinary Investigation". *International Journal of Cosmetic Science* 36(5): 459-70. https://doi.org/10.1111/ics.12148.

Corley, R.A., S.A. Saghir, M.J. Bartels, S.C. Hansen, J. Creim, K.E. McMartin, and W.M. Snellings. 2011. "Extension of a PBPK Model for Ethylene Glycol and Glycolic Acid to Include the Competitive Formation and Clearance of Metabolites Associated with Kidney Toxicity in Rats and Humans". *Toxicology and Applied Pharmacology* 250 (3): 229-44. https://doi.org/10.1016/j.taap.2010.10.011.

Demoulin, Nathalie, Selda Aydin, Valentine Gillion, Johann Morelle, and Michel Jadoul. 2022. "Pathophysiology and Management of Hyperoxaluria and Oxalate Nephropathy: A Review". *American Journal of Kidney Diseases* 79 (5): 717-27. https://doi.org/10.1053/j.ajkd.2021.07.018.

Ding, Tao, Tingting Zhao, Yinhui Li, Zhixiao Liu, Jiarong Ding, Boyao Ji, Yue Wang, and Zhiyong Guo. 2021. "Vitexin Exerts Protective Effects against Calcium Oxalate Crystal-Induced Kidney Pyroptosis in Vivo and in Vitro". *Phytomedicine* 86 (juin):153562. https://doi.org/10.1016/j.phymed.2021.153562.

ECHA (European Chemicals Agency). 2024b. *Guidance on Information Requirements and*

Chemical Safety Assessment: Chapter R.7c: Endpoint Specific Guidance. LU: Publications Office. https://data.europa.eu/doi/10.2823/95811.

ECHA (European Chemicals Agency). 2018. Committee for Risk Assessment RAC opinion proposing harmonised classification and labelling at EU level of glyoxylic acid…%. CLH-O-0000001412-86-204/F

EFSA. Buist, Harrie, Peter Craig, Ian Dewhurst, Susanne Hougaard Bennekou, Carsten Kneuer, Kyriaki Machera, Christina Pieper, et al. 2017 "Guidance on Dermal Absorption". *EFSA Journal*.

Fowles, Jeff, Marcy Banton, Joanna Klapacz, and Hua Shen. 2017. "A Toxicological Review of the Ethylene Glycol Series: Commonalities and Differences in Toxicity and Modes of Action". *Toxicology Letters* 278 (August):66-83. https://doi.org/10.1016/j.toxlet.2017.06.009.

Garrelfs, Sander F., Serhii Chornyi, Heleen te Brinke, Jos Ruiter, Jaap Groothoff, and Ronald J. A. Wanders. 2024. "Glyoxylate Reductase: Definitive Identification in Human Liver Mitochondria, Its Importance for the Compartment-specific Detoxification of Glyoxylate". *Journal of Inherited Metabolic Disease* 47(2): 280-88. https://doi.org/10.1002/jimd.12711.

Gavazzoni Dias, Maria FernandaReis. 2015. "Hair Cosmetics: An Overview". *International Journal of Trichology* 7(1): 2. https://doi.org/10.4103/0974-7753.153450.

Gibbs, Dorothy A., Sunna Hauschildt, and R.W.E. Watts. 1977. "Glyoxylate Oxidation in Rat Liver and Kidney". *The Journal of Biochemistry* 82(1): 221-30. https://doi.org/10.1093/oxfordjournals.jbchem.a131673.

Greenberg, Meidad, Alon Bnaya, and Keren Cohen-Hagai. 2022. "Not Always 'Straight Ahead' – A Surprising Cause of Acute Kidney Injury". *European Journal of Internal Medicine* 106 (décembre):124-25. https://doi.org/10.1016/j.ejim.2022.08.017.

Hatsbach de Paula, Joane Nathache, Flávia Machado Alves Basílio, and Fabiane Andrade Mulinari-Brenner. 2022. "Effects of Chemical Straighteners on the Hair Shaft and Scalp". *Anais Brasileiros de Dermatologia* 97(2): 193-203. https://doi.org/10.1016/j.abd.2021.02.010.

Huber, Aurélie, Christine Deffert, Solange Moll, Sophie de Seigneux, and Lena Berchtold. 2024. "Acute Kidney Injury and Hair-Straightening Products". *Kidney International Reports* 9 (8): 2571-73. https://doi.org/10.1016/j.ekir.2024.06.010.

"Kidney Injury and Hair-Straightening Products Containing Glyoxylic Acid". 2024a. *N Engl j Med*.

Kum, Cavit, Selim Sekkin, Funda Kiral, and Ferda Akar. 2007. "Effects of Xylene and Formaldehyde Inhalations on Renal Oxidative Stress and Some Serum Biochemical Parameters in Rats". *Toxicology and Industrial Health* 23 (2): 115-20. https://doi.org/10.1177/0748233707078218.

Leite, M. G. A., and P. M. B. G. Maia Campos. 2017. "Mechanical Characterization of Curly Hair: Influence of the Use of Nonconventional Hair Straightening Treatments". *Skin Research and Technology* 23 (4): 539-44. https://doi.org/10.1111/srt.12368.

Leite, Marcella Gabarra Almeida, Wanessa Almeida Ciancaglio Garbossa, and Patricia Maria Berardo Gonçalves Maia Campos. 2018. "Hair Straighteners: An Approach Based on Science and Consumer Profile". *Brazilian Journal of Pharmaceutical Sciences* 54 (3). https://doi.org/10.1590/s2175-97902018000317339.

Maneli, Mbulelo H., Peter Smith, and Nonhlanhla P. Khumalo. 2014. "Elevated Formaldehyde Concentration in “Brazilian Keratin Type” Hair-Straightening Products: A Cross-Sectional Study". *Journal of the American Academy of Dermatology* 70(2): 276-80. https://doi.org/10.1016/j.jaad.2013.10.023.

Ming, Shaoxiong, Jia Tian, Ke Ma, Chengbin Pei, Ling Li, Zeyu Wang, Ziyu Fang, et al. 2022. "Oxalate-Induced Apoptosis through ERS-ROS–NF-κB Signalling Pathway in Renal

Tubular Epithelial Cell". *Molecular Medicine* 28(1): 88. https://doi.org/10.1186/s10020-022-00494-5.

Oh, Seung Young, Jong Kyou Kwon, Seo Yeon Lee, Moon Soo Ha, Yong Wook Kwon, and Young Tae Moon. 2011. "A Comparative Study of Experimental Rat Models of Renal Calcium Oxalate Stone Formation". *Journal of Endourology* 25(6): 1057-61. https://doi.org/10.1089/end.2010.0386.

Okada, Atsushi, Shintaro Nomura, Yuji Higashibata, Masahito Hirose, Bing Gao, Mugi Yoshimura, Yasunori Itoh, Takahiro Yasui, Keiichi Tozawa, and Kenjiro Kohri. 2007. "Successful Formation of Calcium Oxalate Crystal Deposition in Mouse Kidney by Intraabdominal Glyoxylate Injection". *Urological Research* 35(2): 89-99. https://doi.org/10.1007/s00240-007-0082-8.

Peteffi, Giovana Piva, Marina Venzon Antunes, Caroline Carrer, Eduarda Trevizani Valandro, Sílvia Santos, Jéssica Glaeser, Larissa Mattos, Luciano Basso da Silva, and Rafael Linden. 2016. "Environmental and Biological Monitoring of Occupational Formaldehyde Exposure Resulting from the Use of Products for Hair Straightening". *Environmental Science and Pollution Research* 23(1): 908-17. https://doi.org/10.1007/s11356-015-5343-4.

Ramos, Camila de Oliveira, Clarissa Rodrigues Nardeli, Keila Karine Duarte Campos, Karina Braga Pena, Dafne Fernandes Machado, Ana Carla Balthar Bandeira, Guilherme de Paula Costa, André Talvani, and Frank Silva Bezerra. 2017. "The Exposure to Formaldehyde Causes Renal Dysfunction, Inflammation and Redox Imbalance in Rats". *Experimental and Toxicologic Pathology* 69 (6): 367-72. https://doi.org/10.1016/j.etp.2017.02.008.

Robert T, Tang E, Kervadec J, Zaworski J, Daudon M, Letavernier E. 2024a. "Kidney Injury and Hair-Straightening Products Containing Glyoxylic Acid". The New England Journal of Medicine 390(12):1147-1149. https://doi.org/10.1056/NEJMc2400528

Robert T, Tang E, Kervadec J, Desmons A, Hautem JY, Zaworski J, Daudon M, Letavernier E. 2024b. "Hair-straightening cosmetics containing glyoxylic acid induce crystalline nephropathy". Kidney International 106(6):1117-1123. https://doi.org/10.1016/j.kint.2024.07.032.

Salido, Eduardo, Angel L. Pey, Rosa Rodriguez, and Victor Lorenzo. 2012a. "Primary Hyperoxalurias: Disorders of Glyoxylate Detoxification". *Biochimica Et Biophysica Acta* 1822 (9): 1453-64. https://doi.org/10.1016/j.bbadis.2012.03.004.

Schnedler, Nina, Gerhard Burckhardt, and Birgitta C. Burckhardt. 2011. "Glyoxylate Is a Substrate of the Sulfate-Oxalate Exchanger, Sat-1, and Increases Its Expression in HepG2 Cells". *Journal of Hepatology* 54(3): 513-20. https://doi.org/10.1016/j.jhep.2010.07.036.

Uyama, Makoto, Shinya Okabe, Takumi Kurashima, Rie Kurinobu, Miwa Takechi, Ryo Yoshiba, Rina Miyoshi, et al. 2023. "Promotion of Glyoxylic Acid Penetration into Human Hair by Glycolic Acid". *International Journal of Cosmetic Science* 45 (2): 246-54. https://doi.org/10.1111/ics.12838.

Zararsiz, I, M Sarsilmaz, U Tas, I Kus, S Meydan, and E Ozan. 2007. "Protective Effect of Melatonin against Formaldehyde-Induced Kidney Damage in Rats". *Toxicology and Industrial Health* 23 (10): 573-79. https://doi.org/10.1177/0748233708089022.

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ANSES. (2025). OPINION of the French Agency for Food, Environmental and Occupational Health & Safety on the review of knowledge of the renal toxicity of glyoxylic acid found in hair-straightening products. (Request No 2024-AUTO-0079). Maisons-Alfort: ANSES, 40 p.

ANNEX 1

Presentation of the participants

PREAMBLE: The expert members of the Expert Committees and Working Groups or designated rapporteurs are all appointed in a personal capacity, *intuitu personae*, and do not represent their parent organisation.

RAPPORTEURS (IF APPLICABLE)

Ms Laëtitia KOPPE-GUICHARD – University Lecturer-Hospital Practitioner (Lyon Sud Hospital, Hospices Civils de Lyon) – Expertise: nephrology, nutrition, low-protein diet, probiotics, prebiotics, chronic kidney disease, nephroprotection

Mr Ludovic LE HEGARAT – Deputy Head of Unit, Toxicology of Contaminants (Fougères Laboratory – ANSES) – Expertise: genotoxicity, toxicology, toxicity reference values, hepatotoxicity, metabolism

Mr Sylvaine RONGA-PEZERET – Toxicology Doctor, Health Risk Assessor (EDF – Medical Studies Department) – Expertise: medicine, toxicology, risk assessment

EXPERT COMMITTEE

The work was monitored and adopted by the following Expert Committee:

- CES on "Chemicals covered by the REACh and CLP Regulations" *(fifth term, from 1 September 2024 to 31 August 2028)*

Chair

Mr Christophe MINIER – University Professor – Le Havre University, Normandy

Vice-Chairs

Mr Fabrizio PARISELLI – Research Engineer, Toxicologist – CNRS

Ms Sylvie ROSSET – University Professor (University of Picardy Jules Verne) – Expertise: analytical chemistry and risk assessment

Members

Ms Isabelle BILLAULT – Lecturer (Paris-Saclay University) – Expertise: organic chemistry, analytical chemistry, physico-chemical properties of substances

Mr Fabien BRETTE – Research Officer (Inserm, University of Montpellier, CNRS) – Expertise: cardiovascular physiology, in vitro and in vivo models, ecotoxicology, environment

Mr Christophe CALVAYRAC – Lecturer (University of Perpignan Via Domitia) – Expertise: analytical chemistry, environmental fate, biotic and abiotic degradation, microbiology, microbial ecology

Mr Sébastien ELIS – Research Director (INRAE, Centre Val de Loire, Nouzilly) – Expertise: reproductive biology (ovaries, oocytes, lipid metabolism, bisphenols, female reproduction, PFAS)

Mr Benjamin EVEN – Lecturer (University of Paris-Est Créteil – UPEC) – Expertise: ageing, toxicology, cellular and molecular signalling

Mr Pascal FROMENT – Research Director (INRAE, Centre Val de Loire, Nouzilly) – Expertise: reproductive biology (gonads, testicular function, endocrine disruptors, avian, rodent and human models)

Ms Aurore GELY-PERNOT – Lecturer (EHESP-IRSET, Rennes) – Expertise: reproductive biology, pesticides, toxicology, environmental health, endocrine disruptors

Ms Laure GEOFFROY – Ecotoxicologist (Ineris) – Expertise: environment, ecotoxicology, nanomaterials, endocrine disruptors

Ms Aurélie GOUTTE – Lecturer (EPHE higher education and research institution – UMR METIS – Sorbonne University, Paris 5) – Expertise: pesticides, pharmaceutical residues, phthalates, endocrine disruption, fish, transfers of resource substances

Ms Catherine GROSDEMANGE-BILLIARD – Professor of Chemistry (University of Strasbourg) – Expertise: organic and analytical chemistry, method analysis, antimicrobials, nanomaterials

Mr Ludovic LE HEGARAT – Deputy Head of Unit, Toxicology of Contaminants (Fougères Laboratory – ANSES) – Expertise: genotoxicity, toxicology, toxicity reference values, hepatotoxicity, metabolism

Mr Nicolas LOISEAU – Research Director (INRAE) – Expertise: chemistry, toxicology, hepatotoxicology, QSAR, pharmacology

Mr Jean-François MASFARAUD – Lecturer (University of Lorraine, CNRS) – Expertise: ecotoxicology/toxicology, risk studies, contaminants, hazard assessment

Mr Christophe MINIER – University Professor (Le Havre University, Normandy) – Expertise: ecotoxicology, regulatory context, endocrinology, endocrine disruptors

Mr Thierry ORSIERE – Research Engineer authorised to supervise research (HDR) (Aix-Marseille University) – Expertise: genetic toxicology

Mr Fabrizio PARISELLI – Research Engineer, Toxicologist (CNRS) – Expertise: toxicology, regulations, occupational health and safety, risk assessment

Ms Cécile QUANTIN – University Professor (Paris Sud University) – Expertise: soil contamination, isotope tracing, metals, PAHs, environmental geochemistry

Ms Sophie ROBERT – Expert Consultant on chemical and toxicological risks in occupational health (INRS, Paris) – Expertise: chemical and biocidal product regulations, prevention of occupational chemical risks, worker safety, sector studies

Mr Sylvaine RONGA-PEZERET – Toxicology Doctor, Health Risk Assessor (EDF – Medical Studies Department) – Expertise: medicine, toxicology, risk assessment

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Mr Bernard SALLES – Emeritus Professor at the University of Toulouse – Expertise: toxicology, environment and health, carcinogenesis, NAMs

Ms Pascale TALAMOND – Engineer (IRD, ISE-M, University of Montpellier II) – Expertise: biological chemistry, environmental chemistry, chemical characterisation, biomarkers of human activities

Ms Paule VASSEUR – Emeritus Professor of Toxicology at the University of Lorraine, Researcher, Toxicologist and Ecotoxicologist – Expertise: toxicology, public health, environmental health, health risk assessment

Ms Catherine VIGUIE – Research Director, Veterinary (INRAE) – Expertise: endocrinology, endocrine disruptors, toxicology, pharmacology

ANSES PARTICIPATION

Scientific coordination

Ms Pauline GUILLOU – Scientific Expert Appraisal Coordinator, Cosmetics and Tattoo Products, Unit for Assessment of Chemical Reference Values and Risks (UEVRRiSC)

Scientific contribution

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Ms Pauline GUILLOU – Scientific Expert Appraisal Coordinator, Cosmetics and Tattoo Products, Unit for Assessment of Chemical Reference Values and Risks (UEVRRiSC)

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Ms Sarah AOUAD – Research Officer, DAVS

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Tenon Hospital – AP-HP (Paris)

Professor Emmanuel LETAVERNIER – Nephrologist – Multidisciplinary Functional Explorations Department – Tenon Hospital – AP-HP

Conception Hospital – AP-HM (Marseille)

Professor Thomas ROBERT – Nephrologist – Nephrology and Kidney Transplant Centre – Conception Hospital – AP-HM

ANNEX 2: METHODOLOGY FOR THE LITERATURE SEARCH

A literature search was carried out to answer the following specific questions:

1. In what categories of cosmetic products is glyoxylic acid found?
2. Have there been reports of kidney injury following exposure to hair-straightening products?
3. Can glyoxylic acid cause kidney injury?

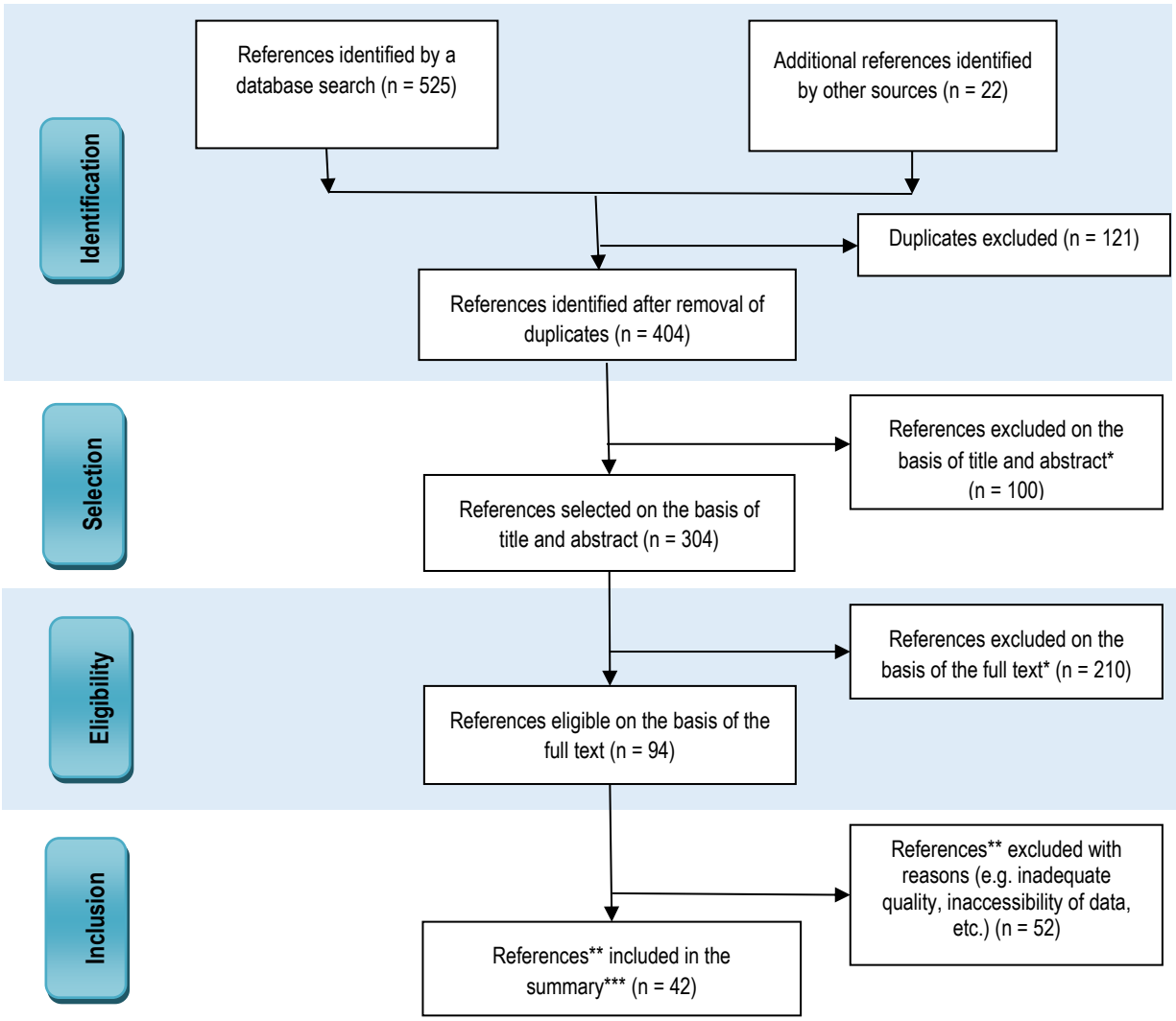
The query was carried out on two databases: PubMed (search on "Title/Abstract") and Scopus (search on "TITLE-ABS-KEY") between February and May 2024, with no date limit. An update was carried out in November 2024.

Question	Key words	Total number of identified publications
1	"glyoxylic acid" AND cosmetic*	23
2	"hair straightening" AND kidney	18
3	"glyoxylic acid" AND kidney	484

In total, with the two queries and after removal of duplicates, 382 publications were identified. Twenty-two additional publications were selected from other sources.

Each literature reference was selected on the basis of title and abstract, retaining only studies mentioning glyoxylic acid, renal toxicity studies, data on metabolism and clinical cases. Three hundred and four publications were deemed relevant on the basis of title and abstract.

The full-text assessment resulted in 94 eligible references. In the end, based on this literature search, 42 publications were selected for inclusion in the report.



** if useful, specify the reasons for exclusion or the number of references excluded for each exclusion reason*

*** if relevant to the needs of the expert appraisal method, report the number of studies instead of the number of references*

**** explain whether it is a qualitative or quantitative summary or possibly two separate summaries*

Figure 3: Flow chart[29]

[29] According to Gedda M. (2015). French translation of the PRISMA reporting guidelines for writing and reading systematic reviews and meta-analyses. *Kinésithérapie* 15(157):39-44. doi:10.1016/j.kine.2014.11.004

ANNEX 3: CASES OF ACUTE KIDNEY INJURY OCCURRING AFTER THE USE OF HAIR-STRAIGHTENING PRODUCTS

	Reference	Country	Sex, age (years)	History	Symptoms	Time between application of the hair-straightening product and onset of symptoms	Renal biopsy	Hair-straightening product used
1	Huber et al., 2024	Switzerland	F, 42	None	Asthenia, nausea, vomiting, flank pain	Not specified	Numerous calcium oxalate deposits	Unknown
2	Robert et al., 2024 Cosmetovigilance scheme	France	F, 26	None	Vomiting, diarrhoea, fever, back pain, burning and scalp ulcers	1-3 hours	Not performed	Hanene Lissage Coiffure l'EQUILIBRE containing 8% glyoxylic acid
3	Cosmetovigilance scheme (2024) Unpublished cases	France	F, 38	None	Nausea, asthenia, anorexia, myalgia, headache, thirst	4 hours	Not performed	Ines Lissage Hairstylist Nano Spiruline 1 Anti-frizz Mask containing 9% glyoxylic acid and 0.00065% glycolic acid
4			F, 42	None	Lower back pain, discomfort, nausea	Within hours of application	Not performed	Protéine Bio Organique Soie AmlaNano Liss Hair containing 20% glyoxylic acid

5	Bnaya et al., 2023	Israel	F, 24	None	Abdominal pain, nausea	The time between exposure and symptoms reported in the publication ranged from 1 to 3 hours, depending on the case	Not performed	Unknown
6			F, 22	None	Abdominal pain, nausea, vomiting, scalp rash		Not performed	Keratin-based product[30]
7			F, 30	Nephrolithiasis	Nausea, vomiting, flank pain, scalp rash		Not performed	Keratin-based product
8			F, 29	None	Nausea, vomiting, scalp rash		Not performed	Unknown
9			F, 21	Epilepsy	Abdominal pain, vomiting, migraine, scalp rash		Three oxalate crystals in the tubules	Unknown
10			F, 58	None	Nausea, flank pain, syncope		2.9 oxalate crystals per glomerulus	Keratin-based product
11			F, 14	None	Nausea, flank pain, migraine		Not performed	Unknown
12			F, 31	Smoker	Abdominal pain, vomiting, diarrhoea		Not performed	Unknown

[30] According to the authors: formaldehyde-free products, known to contain glycolic acid derivatives

13			F, 29	Nephrolithiasis	Vomiting, scalp rash		Not performed	Unknown
14			F, 52	Psoriasis, nephrolithiasis	Abdominal and flank pain, nausea, vomiting		Not performed	Unknown
15			F, 24	None	Abdominal pain, nausea, fever		Not performed	Keratin-based product
16			F, 33	None	Nausea, vomiting, chills		Not performed	Keratin-based product
17			F, 17	None	Abdominal pain, nausea, vomiting, fever, scalp rash		Not performed	Keratin-based product
18			F, 24	None	Abdominal pain, nausea, vomiting, scalp rash		Not performed	Unknown
19			F, 36	None	Nausea, vomiting, scalp rash		Not performed	Unknown
20			F, 21	None	Abdominal pain, nausea, vomiting		Not performed	Unknown

21			F, 19	None	Nausea, flank pain, migraine		1.18 oxalate crystals per glomerulus	Unknown
22			F, 44	State of hypercoagulability	Vomiting, flank pain		Not performed	Unknown
23			F, 50	None	Nausea, vomiting		Not performed	Unknown
24			F, 21	None	Nausea, vomiting, flank pain, scalp rash		Not performed	Keratin-based product
25			F, 28	Atopic dermatitis, gastro-oesophageal reflux	Nausea, vomiting, flank pain, scalp rash		Not performed	Keratin-based product
26			F, 32	None	Abdominal pain, nausea, vomiting		2.2 oxalate crystals per glomerulus	Keratin-based product
27			F, 30	None	Flank pain		Not performed	Unknown
28	Bnaya et al., 2023; Abu-Amer et al., 2022		F, 41	Hypothyroidism, gastrectomy	Nausea, vomiting		1.3 oxalate crystals per glomerulus	Keratin-based product including the following ingredients: glyoxyloyl carbocysteine, glyoxyloyl keratin amino acid, propylene

								glycol glycerin, phenoxyethanol, ethylhexylglycerin, disodium and other collagens, surfactants and fragrances
29	Bnaya et al., 2023; Mitler et al., 2021		F, 13	None	Abdominal pain, vomiting, nausea		Microcalcifications in the tubular epithelium	Unknown
30	Bnaya et al., 2023; Greenberg et al., 2022	Israel	F, 16	Psoriasis	Abdominal pain, nausea, vomiting	"Immediately"	8.1 oxalate crystals per glomerulus	Keratin-based product
31	Ahmed et al., 2019	Egypt	F, 10	None	Vomiting, erythema and inflammation of the scalp, tachycardia, dyspnoea, hypertension	1 week	Yes Tubulointerstitial nephritis No information on the presence or absence of crystals	"Formaldehyde-free" product containing the following ingredients: Bis-cetearyl amodimethicone, cyclopentasiloxane, behentrimonium methosulfate, disodium EDTA, keratin, collagen, fragrances and tonics
32			F, 17	None	Vomiting, scalp rash	Not specified		
33	Exchanges with the Israeli Ministry of Health Unpublished cases reported between	Israel	F, 28	No information	Stomach and lower back pain, scalp sores	Not specified	Not specified	Product name not specified, but according to the Israeli Ministry of Health, glyoxylic acid was mentioned on the product label

34	September 2022 and September 2024		F, 16	No information	Scalp rash, stomach pain	1 hour	Not specified	Product name not specified, but contains a glyoxylic acid derivative according to the Israeli Ministry of Health
35			F, 26	No information	No information	Not specified	Not specified	Product name not specified, but according to the Israeli Ministry of Health, glyoxylic acid was mentioned on the product label The product was also tested in a laboratory and found to contain 0.156 ppm glyoxylic acid and 1 ppm formaldehyde, with a pH of 0.92
36			F, 37		Weakness, nausea, tingling in the fingertips, discomfort	During and after the hair-straightening process	Not specified	Product name not specified, but according to the Israeli Ministry of Health, a glyoxylic acid derivative was mentioned on the product label The products were also tested in a laboratory and found to contain:

								- 1100 ppm glyoxylic acid and 6060.5 ppm formaldehyde, with a pH of 0.95 - 1280 ppm glyoxylic acid and < 1 ppm formaldehyde, with a pH of 0.97
37			F, 24	No information	Pain, nausea, scalp excretions	Not specified	Not specified	Unknown product, not registered
38			F, 23	No information	Pain in the waist and lower back, vomiting	Not specified	Not specified	Product name not specified, but contains a glyoxylic acid derivative according to the Israeli Ministry of Health The product was also tested in a laboratory and found to contain 18.46% glyoxylic acid and < 1 ppm formaldehyde, with a pH of 0.85
39			F, 26	No information	Dandruff	Not specified	Not specified	Product name not specified, but contains ammonium thioglycolate according to the Israeli Ministry of Health

40			F, 30	No information	Stomach pain and nausea	Not specified	Not specified	Product name not specified, but contains a glyoxylic acid derivative according to the Israeli Ministry of Health
41			F, 21	No information	Vomiting during the hair-straightening procedure and the following day, and stomach pain	During the hair-straightening procedure and the following day	Not specified	Product name not specified, but contains a glyoxylic acid derivative according to the Israeli Ministry of Health The product was also tested in a laboratory and found to contain 23.715% glyoxylic acid and < 1 ppm formaldehyde, with a pH of 0.94
42			F, 15	No information	Headache, stomach pain and vomiting	2 hours	Not specified	Product name not specified, but contains a glyoxylic acid derivative according to the Israeli Ministry of Health The product was also tested in a laboratory and found to contain 16.83% glyoxylic acid and < 1 ppm

								formaldehyde, with a pH of 1.18
43			No information	No information	No information	No information	Not specified	Product name not specified, but contains a glyoxylic acid derivative according to the Israeli Ministry of Health The product was also tested in a laboratory and found to contain 25.35% glyoxylic acid and < 1116 ppm formaldehyde, with a pH of 0.82
44			F, 15	No information	Stomach pain, nausea	No information	Not specified	Product name not specified, but contains a glyoxylic acid derivative according to the Israeli Ministry of Health
45			F, 28	No information	Vomiting and back pain	No information	Not specified	Product name not specified, but contains a glyoxylic acid derivative according to the Israeli Ministry of Health
46			F, 37	No information	Stomach pain, vomiting	No information	Not specified	Product name not specified, but contains a glyoxylic acid derivative according to

								the Israeli Ministry of Health The product was also tested in a laboratory and found to contain 18.7% glyoxylic acid and < 1 ppm formaldehyde, with a pH of 1.07

ANNEX 4: STAGED CLASSIFICATION OF ACUTE KIDNEY INJURY

	Staging criteria for acute kidney injury (KDIGO 2012)	
Stage	**Increase in serum creatinine**	**Decrease in urine output**
1	≥ 0.3 mg/dL (26.52 µmol/L) or 1.5-1.9 times baseline	< 0.5 mL/kg/h for 6-12 h
2	2-2.9 times baseline	< 0.5 mL/kg/h for ≥ 12 h
3	≥ 4.0 mg/dL (353.60 µmol/L) or ≥ 3 times baseline	< 0.3 mL/kg/h for ≥ 24 hours or anuria for ≥ 12 h

* Data according to Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group: KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney Int Suppl. 2:1-138, 2012.

ANNEX 5: CAUSALITY ASSESSMENT TABLE

Symptomatology	**Suggestive of the use of the cosmetic product**			**Not (very) suggestive of the use of the cosmetic product**		
Time between exposure and onset of symptoms	R and/or AE +	R and/or AE ?	R and/or AE -	R and/or AE +	R and/or AE ?	R and/or AE -
Compatible	Very likely	Likely	Possible	Likely	Possible	Unlikely
Not very compatible / Unknown	Likely	Possible	Unlikely	Possible	Unlikely	Unlikely
Incompatible	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded

R: re-exposure (R (+, positive): the initial symptoms recurred with the same or greater intensity when the user was re-exposed to the product; R (?): when there was no re-exposure to the product or if the re-exposure conditions were not the same as for the initial exposure; R (-, negative): the manifestation did not recur when the user was re-exposed to the product)

AE: Additional examination (AE (+): positive; AE (-): negative; AE (?): if no examination was carried out or in the event of doubtful results