Amended Safety Assessment of Oxyquinoline and Oxyquinoline Sulfate as Used in Cosmetics

Status:	Draft Amended Report for Panel Review
Release Date:	May 16, 2025
Panel Meeting Date:	June 9 – 10, 2025

The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.D.; Samuel M. Cohen, M.D., Ph.D.; Curtis D. Klaassen, Ph.D.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; and Susan C. Tilton, Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D., and the Senior Director is Monice Fiume, M.B.A. This safety assessment was prepared by Priya Ferguson, M.S., Senior Scientific Analyst/Writer, CIR.

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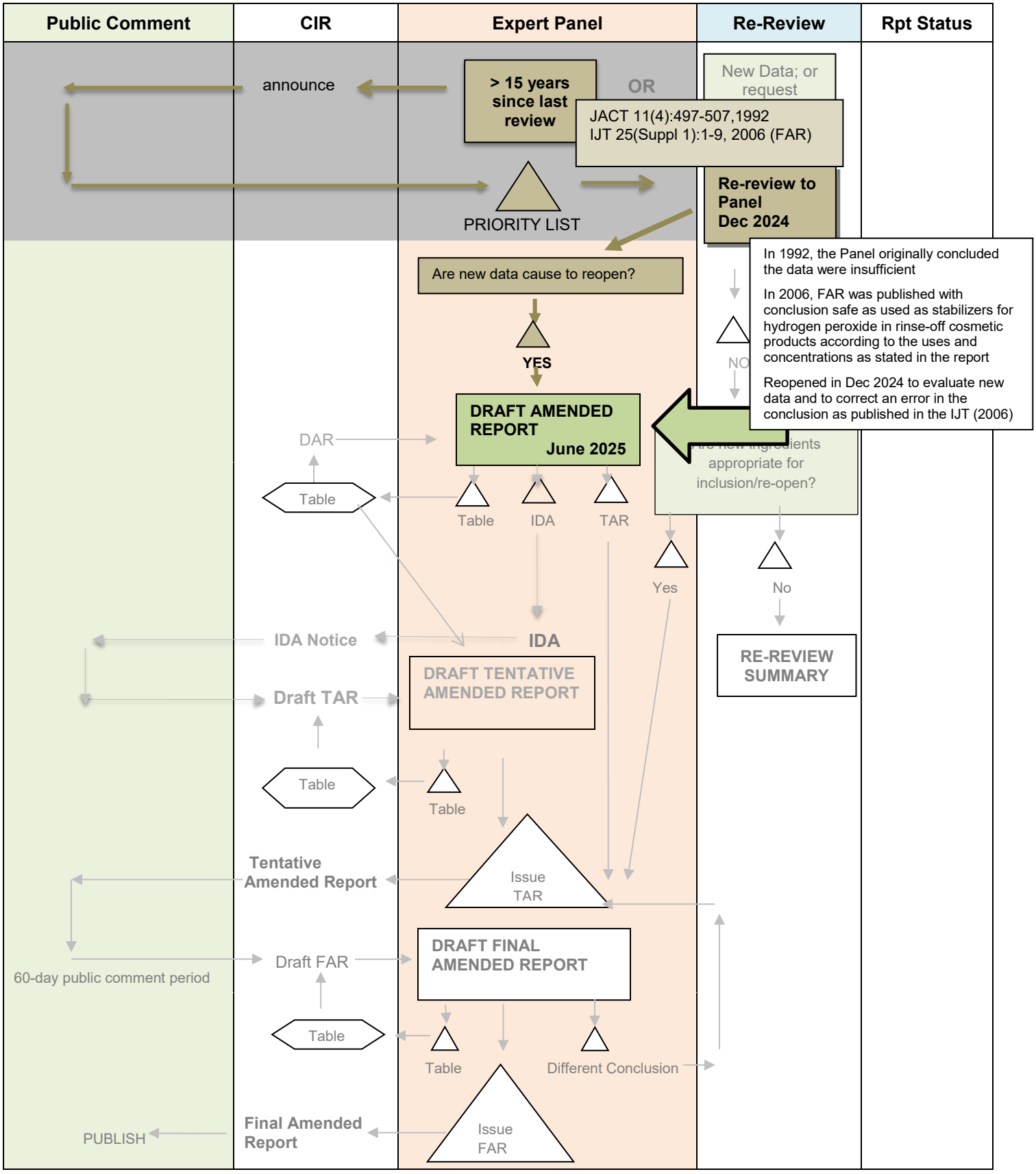
RE-REVIEW FLOW CHART

INGREDIENT/FAMILY Oxyquinoline and Oxyquinoline Sulfate

MEETING June 2025



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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Priya Ferguson, M.S.
Senior Scientific Analyst/Writer, CIR
Date: May 16, 2025
Subject: Draft Amended Report on the Safety Assessment of Oxyquinoline and Oxyquinoline Sulfate

The Expert Panel for Cosmetic Ingredient Safety (Panel) first published a review of the safety of Oxyquinoline and Oxyquinoline Sulfate in 1992 (identified as *originalreport1992_Oxyquinoline_062025* in the pdf). The Panel concluded that there were insufficient data to conclude on the safety of these ingredients. In 2001, additional data were submitted and in 2006, the Panel published a Final Amended Report (identified as *amendedreport2006_Oxyquinoline_062025* in the pdf) on these ingredients; according to the Discussion, the Panel concluded that Oxyquinoline and Oxyquinoline Sulfate are safe as used as stabilizers for hydrogen peroxide in rinse-off cosmetic products according to the uses and concentrations as stated in that report. However, in the published 2006 report, the Conclusion incorrectly states that Oxyquinoline and Oxyquinoline Sulfate are safe as used as stabilizers for hydrogen peroxide in ***leave-on*** cosmetic products. This was a typographical error, as it should instead say that these ingredients are safe as used as stabilizers for hydrogen peroxide in ***rinse-off*** products. This error is further evidenced by the fact that the conclusion of the 2006 report also states there are insufficient data to support the safety of Oxyquinoline and Oxyquinoline Sulfate in leave-on cosmetic products.

Because it had been at least 15 years since the amended report was published, in accordance with Cosmetic Ingredient Review (CIR) Procedures, the Panel re-reviewed these ingredients at the December 2024 meeting. At that meeting, the Panel determined to re-open this safety assessment to evaluate new data and to correct the conclusion from the 2006 report. Thus, a Draft Amended Report on Oxyquinoline and Oxyquinoline Sulfate (*report_Oxyquinoline_062025*) was prepared.

In 2002, Oxyquinoline and Oxyquinoline Sulfate were reported to be used in 4 formulations (at up to 0.1%) and 7 formulations (at up to 0.1%), respectively. According to FDA Registration and Listing Data (RLD; 2024), Oxyquinoline is used in 11 formulations and Oxyquinoline Sulfate is used in 575 formulations. In 2023, FDA VCRP data indicated that Oxyquinoline and Oxyquinoline Sulfate were used in 1 formulation and 19 formulations, respectively. No concentrations of use were reported for Oxyquinoline according to a 2023 survey performed by Council; however, according to this survey, the concentration of use for Oxyquinoline Sulfate has slightly increased since 2002 (it is now reported to be used at up to 0.15%).

Supporting documents for this report package include a flow chart (*flow_Oxyquinoline_062025*), report history (*history_Oxyquinoline _062025*), a search strategy (*search_ Oxyquinoline_062025*), a data profile (*dataprofile_Oxyquinoline_062025*), minutes from the meetings at which the original reports were discussed (*originalminutes_Oxyquinoline_062025*), and transcripts from the recent meeting at which reopening this report was discussed (*transcripts_Oxyquinoline_062025*).

If no further data are needed, the Panel should formulate an updated Discussion and issue a Tentative Amended Report. However, if additional data are required, the Panel should be prepared to identify those needs and issue an Insufficient Data Announcement.

Oxyquinoline and Oxyquinoline Sulfate – History

November 1990

-IDA issued for both ingredients; data needed include: dermal carcinogenicity data in mice, human skin irritation data, sensitization data, and phototoxicity/photosensitization data

August 1991

-Panel issued Tentative Final Insufficient Data report with the conclusion that "The CIR Expert Panel concludes that the available data are insufficient to support the safety of Oxyquinoline and Oxyquinoline Sulfate as used in cosmetic products"

November 2001

-Panel re-opened report due to newly received studies (HRIPT and new studies suggesting that dermal carcinogenicity data is not needed)

June 2002

-Final Amended Report issued with the following conclusion: "The CIR Expert Panel concludes that Oxyquinoline and Oxyquinoline Sulfate are safe as used in stabilizers for hydrogen peroxide in rinse-off hair care products. The available data are insufficient to support the safety of these ingredients in leave-on cosmetic products. The data that are needed in order for the Panel to complete its safety assessment are: (1) impurities data and (2) UV absorption data; if absorption occurs, then photorritation/photosensitization data will be needed."

2006

-Final Amended Report published; in the published 2006 report, the Conclusion incorrectly states that Oxyquinoline and Oxyquinoline Sulfate are safe as used as stabilizers for hydrogen peroxide in ***leave-on*** cosmetic products. This was a typographical error, as it should instead say that these ingredients are safe as used as stabilizers for hydrogen peroxide in ***rinse-off*** products.

December 2024

-Panel re-reviews ingredients and decides to re-open due to evaluate new data and correct conclusion form 2006 report

June 2025

-Panel reviews Draft Amended Report

Oxyquinoline and Oxyquinoline Sulfate Data Profile* – June 2025 – Writer, Priya Ferguson																														
	Use				Toxico-kinetics			Acute Tox			Repeated Dose Tox			DART		Genotox		Carci		Dermal Irritation			Dermal Sensitization				Ocular Irritation		Clinical Studies	
	New Rpt	Old Rpt	Method of Mfg	Impurities	log P/log K_{ow}	Dermal Penetration	ADME	Dermal	Oral	Inhalation	Dermal	Oral	Inhalation	Dermal	Oral	In Vitro	In Vivo	Dermal	Oral	In Vitro	Animal	Human	In Vitro	Animal	Human	Phototoxicity	In Vitro	Animal	Retrospective/ Multicenter	Case Reports
Oxyquinoline	**X**	**O**	**O**		X		OX	X	OX	O		OX			X	OX	OX	O			OX							OX	X	X
Oxyquinoline Sulfate	**X**	**O**						X	X							OX				X			X		OX		X			X

* “X” indicates that new data were available in this category for the ingredient; “O” indicates that data from the original assessment were available

Oxyquinoline and Oxyquinoline Sulfate

Ingredient	CAS #	PubMed	FDA	CompTox	ChemPort	NIOSH	NTIS	NTP	FEMA	EU	ECHA	SIDS	SCCS	AICIS	FAO	WHO	Web
Oxyquinoline	148-24-3	X	X	X	X					X	X			X			X
Oxyquinoline Sulfate	134-31-6	X	X		X					X	X			X			X

X = useful data found

Search Strategy

Searches were performed for 2001 forwards using the following search terms on the websites listed below:
-(Oxyquinoline) or (141-24-3)

-(Oxyquinoline Sulfate) or (134-31-6)

LINKS

Search Engines

- Pubmed - http://www.ncbi.nlm.nih.gov/pubmed
  - appropriate qualifiers are used as necessary
  - search results are reviewed to identify relevant documents
- CompTox: https://comptox.epa.gov/dashboard/chemical/pubmed-abstract-sifter/DTXSID3039242; https://www.epa.gov/comptox-tools/downloadable-computational-toxicology-data#LM
- eChemPortal: https://www.echemportal.org/echemportal/
- DeepDyve: https://www.deepdyve.com/
- Connected Papers - https://www.connectedpapers.com/

Pertinent Websites

- wINCI - https://incipedia.personalcarecouncil.org/winci/ingredient-custom-search/
- FDA Cosmetics page - https://www.fda.gov/cosmetics
- eCFR (Code of Federal Regulations) - https://www.ecfr.gov/
- FDA search databases: https://www.fda.gov/industry/fda-basics-industry/search-databases
- Substances Added to Food (formerly, EAFUS): https://www.fda.gov/food/food-additives-petitions/substances-added-food-formerly-eafus
- GRAS listing: https://www.fda.gov/food/food-ingredients-packaging/generally-recognized-safe-gras
- SCOGS database: https://www.fda.gov/food/generally-recognized-safe-gras/gras-substances-scogs-database
- Inventory of Food Contact Substances Listed in 21 CFR: https://www.cfsanappsexternal.fda.gov/scripts/fdcc/index.cfm?set=IndirectAdditives
- Drug Approvals and Database: https://www.fda.gov/drugs/development-approval-process-drugs/drug-approvals-and-databases
- FDA Orange Book: https://www.fda.gov/drugs/drug-approvals-and-databases/approved-drug-products-therapeutic-equivalence-evaluations-orange-book
- OTC Monographs - https://dps.fda.gov/omuf; https://dps.fda.gov/omuf/monographsearch
- Inactive Ingredients Approved For Drugs: https://www.accessdata.fda.gov/scripts/cder/iig/
- FEMA (Flavor & Extract Manufacturers Association) GRAS: https://www.femaflavor.org/fema-gras
- NIOSH (National Institute for Occupational Safety and Health) - http://www.cdc.gov/niosh/
- NTIS (National Technical Information Service) - http://www.ntis.gov/
  - technical reports search page: https://ntrl.ntis.gov/NTRL/
- NTP (National Toxicology Program) - http://ntp.niehs.nih.gov/
- EUR-Lex - https://eur-lex.europa.eu/homepage.html
- Scientific Committees (SCCS, etc) opinions: https://health.ec.europa.eu/scientific-committees_en https://health.ec.europa.eu/scientific-committees/scientific-committee-consumer-safety-sccs_en
- ECHA (European Chemicals Agency – REACH dossiers) – https://echa.europa.eu/

- European Medicines Agency (EMA) - http://www.ema.europa.eu/ema/
- OECD SIDS (Organisation for Economic Co-operation and Development Screening Info Data Sets)- http://webnet.oecd.org/hpv/ui/Search.aspx
- EFSA (European Food Safety Authority) - https://www.efsa.europa.eu/en
- ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) - http://www.ecetoc.org
- AICIS (Australian Industrial Chemicals Introduction Scheme)- https://www.industrialchemicals.gov.au/
- International Programme on Chemical Safety http://www.inchem.org/
- Office of Dietary Supplements https://ods.od.nih.gov/
- FAO (Food and Agriculture Organization of the United Nations) - http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/en/
- WHO (World Health Organization) IRIS library - https://apps.who.int/iris/
- a general Google and Google Scholar search should be performed for additional background information, to identify references that are available, and for other general information - www.google.com https://scholar.google.com/

DECEMBER 2024 MEETING – RE-REVIEW

Belsito Team – December 2, 2024

DR. BELSITO: Then next one is oxyquinoline. So, we first published a review of oxyquinoline and oxyquinoline sulfate in '92. Concluded there were insufficient data to conclude the safety. In 2006 we looked and published a final amended report on these ingredients and concluded that they were safe as used as stabilizers for hydrogen peroxide in rinse off cosmetic products according to the uses and concentrations as stated in that report.

The published 2006 report, however, the conclusion incorrectly states that oxyquinoline and oxyquinoline sulfate are safe as used as stabilizers for hydrogen peroxide in leave-on cosmetic products and that was a typo error as it's used as a stabilizer for hydrogen peroxide in rinse off products. So, we have an incorrect conclusion, at least based upon our understanding of the data in 2006. It's been 15 years since the amended report and so we're looking to reevaluate this as to whether we should reopen it.

In October of this year an extensive search of the world's literature was performed from 2001 on and there were additional new data that was found since the last iteration. So, basically, I thought we really needed to reopen this to assess the new data and to look at our old conclusion that was potentially incorrect because we said for the stabilizer for hydrogen peroxide in leave on products rather than rinse off which was our intention.

And that's where I am. Reopen to look at new data and potentially change the conclusion.

DR. SNYDER: I concur, and there was also new dermal/repro data -- Table 6 -- but those weren't at very high levels, so I didn't think they were relevant so, yeah.

DR. BELSITO: Yeah. Curt?

DR. KLAASSEN: Yeah. I go along with that. Definitely need to correct that conclusion.

DR. BELSITO: Okay.

DR. RETTIE: If that was all there was and there was no new data that might raise concerns than just correcting a typo, do we have an alternative way to deal with that? That's just for my own interest here, or would you have to reopen?

DR. HELDRETH: If it was purely editorial and it was just the changing of the word and the meaning didn't change, I'd say sure we could fix that without reopening it. But even though it seems to be like it was mistake where we're talking about giving a definition that has a different meaning to it, I would suggest that it's worth the effort to reopen it. And I don't think it's too much work for too little considering the number of uses that we're seeing of the sulfate in the RLD.

So, I think it's worthwhile to go through the full effort.

DR. RETTIE: Okay.

DR. BELSITO: Yeah. We need to look at the new data. I mean, our conclusion may end up being the same but it's safe in leave ons as well, but we don't know until we really fully reevaluate.

DR. HELDRETH: Right.

DR. BELSITO: Okay.

Cohen Team – December 2, 2024

DR. COHEN: Bear with me, I'm taking notes as we go along. Oxyquinoline and Oxyquinoline Sulfate was published in 1992, and the conclusion was insufficient data to conclude anything on the safety. In 2006, the Panel published a final amended report on these ingredients and concluded that they were safe as used as stabilizers for hydrogen peroxide and rinse-off cosmetic products, according to the uses and concentration stated in that report.

However, the report published in 2006 incorrectly stated that these products were safe as used as stabilizers for hydrogen peroxide in leave-on cosmetics, which is a typographical error.

15 years have gone by. In 2002, we had reported uses of four formulations for the oxyquinoline at 0.1 percent and seven formulations of the sulfate at 0.1 percent. The 2023 VCRP data had 1 and 19 formulations of the two. And the oxyquinoline sulfate was in two lipstick formulations. We have RLD of quite a lot of use for the oxyquinoline sulfate, and two were near the eye. No concentration of use was reported for oxyquinoline in the 2023 survey performed by the Council. However, we have it for the sulfate now up to 0.15 percent.

We have irritation and sensitization at 1 percent. There is nothing for impurities and there's voluminous tox data that have been added here. There was a positive micronucleus study, I wanted you guys to comment on that.
Is this a case for the expanded re-review summary that we discussed this morning?

DR. BERGFELD: I have a question about correcting the conclusion, and maybe Monice can talk about that. This is a decided change in the conclusion.

MS. FIUME: Wilma, I was just thinking about that. I don't think Bart and I have discussed this directly. I think it could be handled in the Discussion of a re-review summary to say that the previously printed conclusion had a typographical error, and it's actually this. But I'm interested to hear what Bart says about that tomorrow. Priya, have you talked with Bart about it to see if it can go that way or does it have to reopen? I don't remember discussing it.

MS. CHERIAN: I feel like we discussed it as part of the summary.

MS. FIUME: As a re-review summary?

MS. CHERIAN: I don't think he said that we had to reopen it, because I do remember asking.

MS. FIUME: Yeah. And I know in the past, like, there is one report that never opened but added ingredients. So it just expanded the conclusion, and that was okay in the past. I think procedurally we should be able to just correct the conclusion. Because if you look at that report, it was obvious what they meant, it was just carried over incorrectly. I believe it can be done as a re-review summary.

DR. BERGFELD: Okay.

DR. COHEN: This is a cosmetic biocide, right. So, the report should have read as a stabilizer for hydrogen peroxide in rinse-off cosmetic products. That's how it should have read. But their 2006 had it as a leave-on.
And then it turns out it winds up in two lipstick formulations, which are leave-on and they're around the mouth.

So the conclusion had material impact on its use it seems, or it was just rogue use. I mean, we see that all the time with the hair dyes. So are we going back to a conclusion of a stabilizer for hydrogen peroxide in leave-on cosmetics? I'm not sure I understand it that well.

MS. FIUME: The rest of that conclusion was the data were insufficient to support safety in leave-on cosmetic products. And insufficient data is not re-reviewed unless someone brings forward new information asking for that insufficient data conclusion to change.

DR. COHEN: Okay. But I guess the question is, is it -- it's just the use question? I think of a stabilizer for a product like peroxide stabilizing, you know, peroxide from decomposing or something happening to it. But we're using a biocide as a stabilizer. What am I missing here?

How is that a stabilizer? Hydrogen peroxide 2 is a biocide. So we're adding a biocide to a biocide. In this case, it's not being used as a biocide, it's being used in the reaction of the rinse-off product. Do you guys, Susan, David, could you explain how that's being used?

DR. ROSS: I haven't looked into that. I don't know if Susan had.

DR. TILTON: No, and I don't know if it's very clear.

DR. ROSS: I mean, for me, when I looked at this, I mean, it's low numbers of uses, but, yeah, you've got the conclusion, that's a bit of an issue that you've discussed already. That has to be clarified. You know, there's a lot of new tox data here. And there's a lot of DART studies, which we didn't have DART in the previous report.

So the way I look at the expanded re-review is update safety info when conclusions are likely to be unchanged. I'm not sure. I hate to reopen anything for lower numbers of uses, but I actually came down as a reopened for this one. But I'm certainly willing to be dissuaded.

DR. COHEN: There's just too many questions.

DR. TILTON: I guess I came to a similar conclusion. Part of it was because of the error in the prior conclusion, the way that it was stated, but also particularly related to the very narrow approval for use. You know, it’s specifically as a stabilizer for hydrogen peroxide, and it’s soft cosmetics. And there are reported uses in the leave-on cosmetics.

And I guess we don't know what that looks like currently with the RLD, but even with the 2023 VCRP data -- I mean, there is a lot of new data. Some of it is supportive of the past data, or is at least consistent with the past data. But we have other data that's new and some of it had positive results.

And so, it could be worth reopening in terms of evaluating that within the narrow approval that was previously provided, and the fact that the conclusion needs to be updated. We previously didn't have the option of the extended re-review, and now it sounds like maybe a conclusion can be changed in the re-review.

MS. FIUME: It could be corrected, yes.

DR. TILTON: Corrected.

DR. ROSS: Again, that's for things where you don't think your conclusion is going to change. Can you make that decision based on what you've got in front of you here?

DR. TILTON: That's right. Which is why I was also leaning towards reopening.

DR. BERGFELD: Belsito opens this on tomorrow.

DR. COHEN: I know. We'll have this discussion one way or the other. We'll bring it up. Are we changing the conclusion? Technically, yes, but in spirit, no, it was a typo. But the thing went out for almost 20 -- right. When did it get back out? Yeah, 18 years and winds up in lipsticks, lip products. I don't know if that's a result of that or not.

And, again, I'm stuck on this. I know they are very pro forma, the use. X and Y are used as blank in cosmetics, Okay? And most of the time it's a skin conditioning agent or a hair conditioning agent. But every now and again I get wrapped around the axle on the use. And I don't understand a biocide being used as a stabilizer for a product that's intrinsically a biocide. We use 2 percent hydrogen peroxide to cleanse wounds. I'm trying to get my head wrapped around this.

DR. BERGFELD: Maybe PCPC can arrange to give us a definition of how it's used and why it's used.

DR. COHEN: All right, we'll bring it up tomorrow.

MS. FIUME: David, I don't know if it matters, but the current functions are also chelating agent.

DR. COHEN: Chelating agent.

MS. FIUME: According to the current functions, is chelating agent and cosmetic biocide.

DR. COHEN: Chelating agent in diagnostic radiopharmaceuticals.

DR. ROSS: That might stop your oxidative changes to the peroxide.

DR. COHEN: I see in the report it says non-cosmetic uses as a chelating agent.

MS. FIUME: In the current wINCI dictionary, chelating agent is a function. I didn't see it in the introduction of the 2006 report, but it currently is described as a chelating agent as well as a biocide.

DR. COHEN: It's in Table 2. It's in Table 2 under prescription OTC therapeutic uses. Non-cosmetic use Table 2.

MS. FIUME: Those are two points where it's pointing to it as a chelating agent, the non-cosmetic use as well as the updated functions in the dictionary.

DR. ROSS: Yeah, the problem with peroxides is they oxidize up. So where you got chelating agents, they're probably going to minimize those oxidative changes. So that's probably getting at why it was used. I mean, there's many other chelating agents you can use, of course, so I don't know why this one. But anyway, it may give us some clues.

DR. COHEN: All right. We got that and we'll discuss it tomorrow. Just a quick question, when is the read-across group meeting again, at 1:00?

MS. FIUME: Yes.

DR. BERGFELD: 1:00 to 1:30.

DR. COHEN: So then we reconvene at 1:30?

DR. BERGFELD: Correct.

DR. COHEN: Susan and David, you're on that committee? It's hard to get ticket to that concert.

DR. ROSS: For our sins, yeah.

DR. COHEN: The question is do you guys want the hour for lunch? You want to go 50 more minutes to bang out another one or two? What do you want to do? Because we won't be reconvening until 1:30.

DR. ROSS: I'm fine with going on a little bit, I don't know what Susan needs to do.

DR. TILTON: I'm fine too. It's not lunchtime here so.

DR. COHEN: Oh yeah, based on the map.

DR. TILTON: Yeah.

Full Panel – December 3, 2024

DR. BELSITO: Yeah. This is a potential re-review opening of the safety of Oxyquinoline and oxyquinoline sulfate in '92. We concluded that the data were insufficient. In 2006, we published a final amended report for these ingredients and we concluded that they were safe as used as stabilizers for hydrogen peroxide and rinse off cosmetic products according to uses and concentrations in that report.

However, there was a typo in the conclusion of that report, and instead we said that these ingredients are safe as used as stabilizers for hydrogen peroxide in rinse off products. Rather, the conclusion was that oxyquinoline were safe as used as stabilizers for hydrogen peroxide in leave-on products, was our conclusion, rather than the rinse off.

Anyway, it's been 15 years since the amended report was published. And so it's up to determine whether we need to reopen it. And also, since that time, there's been a voluminous amount of new data. I thought we needed to reopen to assess the new data and also to possibly change our conclusion to use in rinse-off products. But until we see that new data it would be hard to determine that so. We're saying reopen.

DR. COHEN: Second.

DR. BERGFELD: Any other comments regarding reopening this ingredient? Bart, do you want to comment on the conclusion change?

DR. HELDRETH: No, I agree. It's unfortunate that this typo was in that conclusion and was out there for many years, unchecked. I think even if there wasn't new data to look at, I think it'd be worthwhile to open it just to make the conclusion accurately reflect the Panel's thinking.

DR. COHEN: And this is a biosign (phonetic) and it's described as a stabilizer for hydrogen peroxide. Is it doing that just to prevent organisms from growing and destabilizing the hygiene peroxide? Just wondering. I usually don't get that wrapped around the axle over the function, but it was -- I couldn't understand it that well.

DR. BELSITO: I think we'll understand it when we see the new report, right?

DR. COHEN: Yeah. Good point, Don.

DR. BERGFELD: All right. I guess that ends that conversation. I'm going to call the question to reopen? Those opposing? Abstaining? Seeing none, it is approved. We'll be reopening this ingredient.

Then our next ingredient up for review is Dr. Cohen, 2-Nitro-p-Phenylenediamine.

Oxyquinoline Sulfate – Original Minutes

IDA Issued - November 1990

Oxyquinoline

Dr. Bergfeld described Oxyquinoline as a Wyden ingredient, used as a fungicide in cosmetics in concentrations of 0.1 to 1%. She recommended that Oxyquinoline receive an insufficient evidence for safety conclusion, due to the need for human irritation and sensitization data and genotoxicity studies. The compound is known to absorb ultraviolet light, and so photosensitivity data is needed.

Dr. Hoffmann asked for photoxicity data.

Dr. Schroeter agreed on the insufficient evidence status, and wanted dermal carcinogenicity data. He also remarked on the disparity between oral and dermal toxicity.

Dr. Shank expressed his reservations concerning the appropriateness of the oral toxicity and carcinogenicity models. There is no knowledge of what happens to the compound in the stomach. Because of the strong mutagenic effects of the compound, he requested skin carcinogenicity studies.

Dr. Hoffmann spoke on the concept of structural analysis of compounds as an indicator of carcinogenicity and asked for a correlation for this compound, reasoning that something in the structure led them to ask for skin carcinogenicity data.

Dr. Shank remarked that not enough is known about the link between structure and carcinogenicity, and that the desire for the carcinogenicity data was based on its mutagenic properties.

Dr. Boutwell pointed out that many compounds that were found to be mutagenic were not carcinogenic. He questioned the need for further carcinogenicity testing.

Dr. Hoffmann said that a mouse skin bioassay may constitute

Oxyquinoline Sulfate – Original Minutes

unreasonable time and budget demands and said that empirical evidence for possibile dermal carcinogenicity is needed to request that kind of study.

Dr. McEwen reminded the Panel that skin toxicity testing is very expensive.

Dr. Carlton proposed that Oxyquinoline might be destroyed or deactivated, so that the oral exposure is not representative of the dermal exposure.

Dr. Shank stated that Oxyquinoline may react with something in the skin. Concerning the need for a conceptual line of reasoning for more testing, he cited Oxyquinoline's DNA and cell binding.

Dr. Hoffmann failed to see the Panel's need for the dermal carcinogenicity data.

Dr. Shank offered the possibility that the compound might react with something in the diet.

Dr. McEwen stated that there were intervaginal studies available.

Dr. Schroeter suggested that it may be detoxified when it is absorbed.

Dr. McEwen asked the Panel for the kind of information they were looking for in an 18 month skin painting study. He wanted to know if there were some better way to obtain this information.

Dr. Boutwell stated that there is no substitute for long term testing.

Dr. Schroeter summarized the discussion by saying that there was an agreement on the need for a ruling of insufficient

Oxyquinoline Sulfate – Original Minutes

data, but that there continued to exist a disagreement on the need for dermal carcinogenicity testing.

Dr. Boutwell summarized his argument for long term carcinogenicity data by saying that Oxyquinoline is a mutagen, a DNA binder, a tumor-promoter, and an irritant, and for the report to be thorough, that this data was needed.

Dr. Elder restated the problem with the relevance of oral toxicity and carcinogenicity data relating to the compound's use in cosmetics.

Dr. Bergfeld had a correction of p. 6 of the report.

Dr. Scroeter moved for a conclusion of insufficient evidence because of lack of data for: dermal carcinogenicity in mice, and human skin irritation, sentization, phototoxicity and photosensitization.

Dr. Bergfeld seconded the motion for an Insufficient Data Announcement.

All were in favor of the motion.

August 1991

Oxyquinoline Sulfate – Original Minutes

Oxyquinoline

Dr. Hoffmann began the discussion by recalling that the Panel had voted in favor of issuing an Insufficient Data Announcement on Oxyquinoline at the November 5-6, 1990 Expert Panel Meeting. The data requested in the announcement were as follows: (a) dermal carcinogenesis and, if the results of this study are negative, (b) skin irritation (human), skin sensitization (human), and phototoxicity (human) data. In the meantime, a Russian study (in a Russian cancer journal) was found in the literature. Dr. Hoffmann referred to this study as being very thorough and indicated that the investigators had found that Oxyquinoline was not carcinogenic when applied to mouse skin. Copies of this study were distributed during the meeting. Additionally, Dr. Hoffmann noted that the additional studies requested by the Panel had not been received.

Dr. Boutwell: I would like to call the Panel's attention to the following quote on page 16 (fourth paragraph) of the Oxyquinoline report: "The International Agency for Research on Cancer (1987) concluded that the evidence is inadequate as to the carcinogenicity of Oxyquinoline in animals." Has the Russian publication referred to by Dr. Hoffmann been included in IARC's 1987 evaluation of this compound?

Dr. Hoffmann: The study should have been included in the IARC evaluation because it was done in the 1970's. Concerning IARC's conclusion of inadequate evidence as to the carcinogenicity of Oxyquinoline, this is a typical IARC ruling. IARC has found one chemical to be non-carcinogenic.

Dr. Bergfeld: A summary of the mouse skin carcinogenicity study will have to be incorporated into the text. This study should also be incorporated into the discussion,

since it is somewhat debatable and since there is a quote in the text stating that IARC concluded that evidence is inadequate as to the carcinogenicity of Oxyquinoline in animals. In that the dermal (mouse) carcinogenicity data are available in the literature, the Panel no longer requests this study.

Dr. Elder then clarified that in the discussion, it will be mentioned that during the comment period for the Insufficient Data Announcement, the Russian dermal carcinogenicity study was provided and the Panel deleted its request for a dermal carcinogenicity study.

Dr. Shank noted that some comment needs to be made about the relationship between the cytotoxic dose of Oxyquinoline and its mutagenic dose (i.e. how close the mutagenic dose is to the cytotoxic dose), because cytotoxicity data are not included in the report. If such information is included in any of the original publications on the mutagenicity of Oxyquinoline, then this information should be incorporated into the report. Without this information, the mutagenicity data are not interpretable and are of no use.

Dr. Elder recalled that carcinogenicity data are included in the report, and questioned the relevance of the mutagenicity studies. He agreed that before the issue of cytotoxicity is dealt with, that he would first review the original publications on mutagenicity for any comments concerning cytotoxicity, and in order to verify that the concentrations reported are accurate and whether Oxyquinoline or Oxyquinoline Sulfate was tested. Dr. Elder also agreed to submit his findings to Drs. Shank, Hoffmann, and Boutwell in accordance with their request. The Expert Panel decided that if two of the three Panel members agree with the findings, their comments would be incorporated into

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text; the document would then be mailed to the third Panel member for approval. The next step would be announcement of a Tentative Final Report on Oxyquinoline.

Dr. McEwen also noted that carcinogenicity data are included in the report, and expressed concern as to whether or not the inclusion of comments concerning the cytotoxicity of Oxyquinoline in the report would modify the Panel's conclusion.

Dr. Bergfeld confirmed that the inclusion of such comments in the report would not modify the Panel's conclusion, and that the Panel had already ruled out any concern relating to the potential carcinogenicity of Oxyquinoline.

Dr. Hoffmann recommended that the report on Oxyquinoline is insufficient due to lack of the following data: (a) skin irritation (human), (b) skin sensitization (human), and (c) photosensitization (human). [The Panel members agreed to change one of the tests originally requested from phototoxicity (human) to photosensitization (human).] He also volunteered to run a UV spectrum on Oxyquinoline (solvent = methanol) in his laboratory, the results of which may preclude a human photosensitization test.

The Panel agreed that if the UV spectral analysis is not received within the next month, or if the UV spectrum demonstrates absorption in the UVB or UVA band, then photosensitization data will definitely be requested. Otherwise, the Panel will request only human data on irritation and sensitization. The final request for data needed in order for the Panel to complete its safety assessment of Oxyquinoline will be outlined in the discussion section of the Tentative Final Report.

All Panel members were in favor of issuing a Tentative Final insufficient data report on Oxyquinoline/Oxyquinoline Sulfate with the following conclusion: "The CIR Expert Panel concludes that the available data are insufficient to support the safety of Oxyquinoline and Oxyquinoline Sulfate as used in cosmetic products."

Dr. Bailey stated that he would provide Dr. Elder with updated frequency of use data on Oxyquinoline.

RR Re-Opened – November 2001

A Final safety assessment with an insufficient data conclusion on these ingredients was issued in 1992. The data needed at that time were as follows:

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(1) Dermal carcinogenesis (mouse); if negative, skin irritation (human) and skin sensitization and photosensitization data (human) will be needed

Since the Final Report was issued, human RIPT data and new studies suggesting that a dermal carcinogenicity study is not needed have been received. Dr. Belsito stated that after reviewing these studies, the available data remain insufficient for evaluating the safety of Oxyquinoline and Oxyquinoline Sulfate in cosmetic products.

Dr. Belsito noted that the following data are needed for completion of this safety assessment:
(1) UV absorption data; if absorption occurs, photoirritation/photosensitization data will be needed.
(2) Method of manufacture and impurities

Dr. Marks said that his Team determined that a safe as used conclusion on Oxyquinoline and Oxyquinoline Sulfate could be issued, but also expressed concern over the UV absorption potential of these chemicals. He said that the issue of UV absorption could possibly be addressed by limiting these ingredients to the maximum authorized concentrations (in the finished cosmetic product) for Oxyquinoline and Oxyquinoline Sulfate that have been established by the European Union. These restrictions are included in the industry submission on Oxyquinoline, and are as follows: stabilizer for hydrogen peroxide in rinse-off hair-care preparations (0.3% calculated as base) and stabilizer for hydrogen peroxide in non-rinse-off hair-care preparations (0.03% calculated as base).

Dr. Marks added that, perhaps, the photosensitivity issue would not be as significant if dermal absorption could be addressed by limiting the concentration of Oxyquinoline and Oxyquinoline Sulfate in cosmetics.

The Panel voted in favor of reopening the Final safety assessment on Oxyquinoline and Oxyquinoline Sulfate that was issued in 1992. Drs. Marks, Shank, and Slaga were in favor of the motion to reopen. Drs. Belsito and Snyder were against the motion.

Dr. Andersen noted that the report that is being considered is the Final Report on Oxyquinoline and Oxyquinoline Sulfate (insufficient data conclusion) that was issued in 1992. He said that the Panel's decision to reopen indicates that the Panel now agrees that the available data are sufficient. With this in mind, the Panel will issue a tentative amended conclusion stating that these ingredients are safe at concentrations at or below 0.3% (calculated as the base) as stabilizers for hydrogen peroxide in rinse-off hair-care preparations and at concentrations at or below 0.03% (calculated as the base) as stabilizers for hydrogen peroxide in non-rinse-off hair-care preparations. A 90-day comment period will be observed after the tentative amended report is issued.

June 2002 – Final Amended Report

A Final Safety Assessment with an insufficient data conclusion on Oxyquinoline and Oxyquinoline Sulfate was issued in 1992. The data needed at that time were as follows: (1) Dermal carcinogenesis (mouse); if negative, skin irritation (human) and skin sensitization and photosensitization data (human) will be needed. Subsequently, human RIPT data and new studies suggesting that a dermal carcinogenicity study is not needed were received. However, after further review, it was determined that UV absorption data and method of manufacture and impurities data were needed.

Furthermore, it was suggested that the issue of UV absorption could possibly be addressed by limiting Oxyquinoline and Oxyquinoline Sulfate to the maximum authorized concentrations (in the finished cosmetic product) for these ingredients that have been established by the European Union. Thus, the Panel issued a Tentative Amended Final Report with the following conclusion: The CIR Expert Panel concludes that Oxyquinoline and Oxyquinoline Sulfate are safe as stabilizers for hydrogen peroxide in leave-on hair care products at concentrations of 0.03% or less and in rinse-off hair care products at concentrations of 0.3%, in both cases, calculated as the base.

Dr. Belsito said that his Team agreed that the CIR report does not support the EU restrictions. He added that there is no reason for these restrictions, other than the fact that they were established by the EU, and noted that their basis remains unknown. Dr. Belsito said that it would be a very poor precedent for the Panel to accept a limitation

just because it has been established by a particular group, not knowing the basis for the limitation. Furthermore, he noted that his Team is not knowledgeable of any leave-on hair care products that contain hydrogen peroxide.

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Dr. Snyder reiterated that the Panel does not have data that support the EU restrictions.

Dr. Belsito said that the data reviewed by the Panel do suggest that Oxyquinoline is not a sensitizer at concentrations up to 1.0% in cosmetic products. He also noted that the Panel does not have data on the photosensitization potential of this ingredient (a UV absorber), and, therefore, its use in leave-on products is inappropriate without these data.

Dr. Belsito said that his Team would support the following conclusion: Oxyquinoline and Oxyquinoline Sulfate are safe as used as stabilizers for hydrogen peroxide in rinse-off hair care products. The available data are insufficient for evaluating the safety of these ingredient in leave-on products. The following data would be needed in order to evaluate the safety of these ingredients in leave-on products: (1) impurities data and (2) photosensitization data (at ingredient use concentration in leave-on cosmetic products). Dr. Belsito noted that Oxyquinoline and Oxyquinoline Sulfate are UV absorbers.

Dr. Shank said that Oxyquinoline absorbs light in the UVC region.

Dr. Belsito said that, according to the report text, Oxyquinoline absorbs UV light at 243 and 318 nm.

Dr. Shank was under the impression that a very minor shoulder was noted at 318 nm.

Dr. Andersen said that, unfortunately, the reference does not provide the Panel with enough information to determine the shape of the absorption spectrum. He noted that there is a peak of some sort at 318 nm.

Dr. Bergfeld wanted to know if the Panel needs a UV spectral analysis of Oxyquinoline and Oxyquinoline Sulfate first.

Dr. Belsito said that he would like to see photosensitization data if these compounds are found to be UV absorbers. He added that Oxyquinoline is not a chemical that is routinely screened; therefore, the absence of clinical data does not mean that there is an absence of disease.

Dr. McEwen wanted to know which impurities would be of interest.

Dr. Belsito said that, looking at the method of manufacture, he would be concerned about quinones or phenols that might cause skin depigmentation.

The Panel voted unanimously in favor of issuing an Amended Final Report with the following conclusion: The CIR Expert Panel concludes that Oxyquinoline and Oxyquinoline Sulfate are safe as used as stabilizers for hydrogen peroxide in rinse-off hair care products. The available data are insufficient to support the safety of these ingredients in leave-on cosmetic products. The data that are needed in order for the Panel to complete its safety assessment will be stated in the report discussion as follows:

(1) Impurities data
(2) UV absorption data; if absorption occurs, then photoirritation/photosensitization data will be needed.

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Dr. McEwen agreed to provide the Panel with current use concentration data.

Amended Safety Assessment of Oxyquinoline and Oxyquinoline Sulfate as Used in Cosmetics

Status: Draft Amended Report for Panel Review
Release Date: May 16, 2025
Panel Meeting Date: June 9 – 10, 2025

The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.D.; Samuel M. Cohen, M.D., Ph.D.; Curtis D. Klaassen, Ph.D.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; and Susan C. Tilton, Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D., and the Senior Director is Monice Fiume, M.B.A. This safety assessment was prepared by Priya Ferguson, M.S., Senior Scientific Analyst/Writer, CIR.

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ABBREVIATIONS

CFR	Code of Federal Regulations
CIR	Cosmetic Ingredient Review
Council	Personal Care Products Council
Dictionary	*International Cosmetic Ingredient Dictionary and Handbook*
DMSO	dimethyl sulfoxide
DPRA	direct peptide reactivity assay
ECHA	European Chemicals Agency
FDA	Food and Drug Administration
FOU	frequency of use
GD	gestation days
GHS	globally harmonized system
HRIPT	human repeated-insult patch test
IC_{50}	half-maximal inhibitory concentration
LD_{50}	median lethal dose
l.o.	leave-on
K_{ow}	octanol-water partition coefficient
MoCRA	Modernization of Cosmetics Regulation Act
NA	not applicable
NR	not reported
NOAEL	no-observed-adverse-effect level
OECD	Organisation for Economic Co-operation and Development
OTC	over-the-counter
Panel	Expert Panel for Cosmetic Ingredient Safety
QSAR	quantitative structure-activity relationship
RLD	Registration and Listing Data
r.o.	rinse-off
TG	test guideline
US	United States
VCRP	Voluntary Cosmetic Registration Program

INTRODUCTION

Oxyquinoline and Oxyquinoline Sulfate are heterocyclic compounds that, according to the web-based *International Cosmetic Ingredient Dictionary and Handbook (*wINCI *Dictionary)*, are reported to function in cosmetics as chelating agents and cosmetic biocides.[1] These ingredients were first reviewed by the Expert Panel for Cosmetic Ingredient Safety (Panel) in a report published in 1992.[2] In that report, it was concluded that the data were insufficient to support a conclusion on the safety of these ingredients. Subsequently, data were received and in 2006, the Panel published a Final Amended Report on these ingredients, and according to the Discussion, the Panel concluded that Oxyquinoline and Oxyquinoline Sulfate are safe as used as stabilizers for hydrogen peroxide in rinse-off cosmetic products according to the uses and concentrations as stated in that report.[3] However, in that report, the Conclusion incorrectly states that Oxyquinoline and Oxyquinoline Sulfate are safe as used as stabilizers for hydrogen peroxide in ***leave-on*** cosmetic products. This was a typographical error, as it should instead say that these ingredients are safe as used as stabilizers for hydrogen peroxide in ***rinse-off*** products. This error is further evidenced by the fact that the conclusion of the 2006 report also states there are insufficient data to support the safety of Oxyquinoline and Oxyquinoline Sulfate in leave-on cosmetic products.

In accordance with its Procedures, the Panel evaluates the conclusions of previously issued reports every 15 years, and as it had been at least 15 years since the previous re-review was issued, the Panel again considered a re-review of this ingredient at the December 2024 meeting. At that meeting, the Panel determined that this safety assessment should be re-opened to evaluate new data and correct the error in the conclusion in the 2006 report.

This safety assessment includes relevant published and unpublished data that are available for each endpoint that is evaluated. Published data are identified by conducting an extensive search of the world's literature; a search was last conducted April 2025 for studies dated 2001 forward. A listing of the search engines and websites that are used and the sources that are typically explored, as well as the endpoints that the Panel typically evaluates, is provided on the Cosmetic Ingredient Review (CIR) website (https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; https://www.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

Excerpts from the summaries of the 2006 report are disseminated throughout the text of this re-review document. These data are identified by *italicized text*. (This information is not included in the tables or the Summary section). For complete and detailed information, the 2006 report and 1992 report can be accessed on the CIR website (https://cir-reports.cir-safety.org/).

Much of the data included in this safety assessment was found on the European Chemicals Agency (ECHA)[4,5] website. Please note that the ECHA website provides summaries of information generated by industry, and it is those summary data that are reported in this safety assessment when ECHA is cited**.**

CHEMISTRY

Definition and Structures

According to the *Dictionary*, Oxyquinoline (CAS No. 148-24-3) is a heterocyclic phenol that conforms to the structure in Figure 1.[1, CIR STAFF]

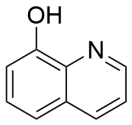

Figure 1. Oxyquinoline

According to the *Dictionary*, Oxyquinoline Sulfate (CAS No. 134-31-6) is the salt of Oxyquinoline and sulfuric acid and conforms to the structure in Figure 2.[1, CIR STAFF]

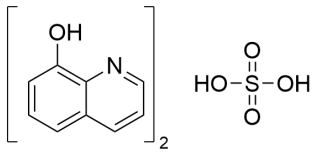

Figure 2. Oxyquinoline Sulfate

These ingredients are the free base and sulfate salt, respectively, of the same monohydroxyquinoline.

Chemical Properties

Oxyquinoline is a white powder or crystalline substance that is virtually insoluble in water or ether, and completely soluble in alcohol, acetone, chloroform, benzene, and aqueous mineral acids.[3] *Oxyquinoline Sulfate is a pale yellow, crystalline powder that is freely soluble in water, and slightly soluble in alcohol.*

Oxyquinoline has a molecular weight of 145.2 g/mol and an octanol-water partition coefficient (K_{ow}) value of 2.02.[3,6] Other chemical properties of Oxyquinoline and Oxyquinoline Sulfate can be found in Table 1.

Method of Manufacture

The methods below are general to the processing of Oxyquinoline, and it is unknown if they apply to cosmetic ingredient manufacturing.

Oxyquinoline

Oxyquinoline can be prepared by the decarboxylation of 8-hydroxyquinoline-4-carboxylic acid.[3] *A second method of manufacture involves heating 2-aminophenol, 2-nitrophenol, and glycerin in sulfuric acid. Quinoline-8-sulfonic acid combines with caustic soda and water, or sulfonation of quinoline with oleum and fusion of the resulting sodium salt with sodium hydroxide will yield Oxyquinoline.*

Composition and Impurities

No composition or impurities data on Oxyquinoline or Oxyquinoline Sulfate were available.

USE

Cosmetic

The safety of the cosmetic ingredients addressed in this assessment is evaluated based on data received from the US Food and Drug Administration (FDA) and the cosmetics industry on the expected use of Oxyquinoline and Oxyquinoline Sulfate in cosmetics. Data included herein were obtained from the FDA and in response to a survey of maximum use concentrations conducted by the Personal Care Products Council (Council), and it is these values that define the present practices of use and concentration. Frequencies of use obtained from the FDA include data from the Voluntary Cosmetic Registration Program (VCRP) database as well as Registration and Listing Data (RLD). As a result of the Modernization of Cosmetics Regulation Act (MoCRA) of 2022, the VCRP was discontinued in 2023 and, as of 2024, manufacturers and processors are required to register facilities and list their products (and ingredients therein) with the FDA (i.e., RLD). An exception is made for small businesses (average gross annual sales in the US of cosmetic products for the previous 3-year period is less than $1,000,000, adjusted for inflation), which are exempt from MoCRA reporting for most cosmetic product categories. Eye area products, injected products, internal use products, or products that alter appearance for more than 24 h, and the facilities that manufacture these products, are not included in this exemption.[7] Please note, at this time, it is not appropriate to contrast data from the VCRP and RLD to determine a trend in frequency of use because there are numerous differences in the ways the data for the VCRP and the RLD were collected and processed, and because reporting frequency of use is now mandatory (as opposed to the past practice of voluntary reporting). Although the VCRP program is now defunct, trends in frequency of use from the RLD alone are not yet possible in that a baseline is currently not available.

In 2002, Oxyquinoline and Oxyquinoline Sulfate were reported to be used at up to 0.1% in 4 and 7 formulations, respectively (Table 2).[3] According to 2023 FDA VCRP data, Oxyquinoline and Oxyquinoline Sulfate were reported to be used in 1 formulation and 19 formulations, respectively.[8] FDA Registration and Listing Data (RLD; 2024) report higher frequencies of use for these ingredients.[9] RLD indicate that Oxyquinoline is used in 11 total formulations and Oxyquinoline Sulfate is reported to be used in 575 total formulations. Oxyquinoline Sulfate is used at up to 0.15% according to 2023 concentration of use data, and no concentrations of use were reported for Oxyquinoline.[3,10]

Incidental ocular exposure to Oxyquinoline Sulfate may occur as this ingredient is reported to be used in formulations that are applied near the eyes. According to 2024 RLD, it is used in 2 eyelash and eyebrow preparations (primers, conditioners, serums, fortifiers; concentration not reported). In addition, Oxyquinoline Sulfate may result in incidental ingestion as it is reported to be used in 2 lipstick formulations, according to 2023 FDA VCRP data (these uses are not reported in 2024 RLD).

Additionally, Oxyquinoline is used in "other fragrance preparations" and could possibly be inhaled (concentration not reported). In practice, as stated in the Panel's respiratory exposure resource document (https://www.cir-safety.org/cir-findings), most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and tracheobronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.

Some products containing Oxyquinoline and Oxyquinoline Sulfate may be marketed for use with airbrush delivery systems. With the advent of MoCRA and the current product categories outlined by the FDA, it is now mandatory that cosmetic products used in airbrush delivery systems be reported as such for some, but not all, product categories in the RLD. In other words, a reliable source of frequency of use data regarding the use of cosmetic ingredients in conjunction with airbrush delivery systems is now available, in some instances. None of the reported product categories for Oxyquinoline and Oxyquinoline Sulfate as listed in the RLD include a designation using airbrush application, so it is possible that these ingredients are used with airbrush delivery

systems, but not reported as such. Additionally, the Council currently surveys the cosmetic industry for maximum reported use concentrations of ingredients in products which may be used in conjunction with an airbrush delivery system; thus, this type of data may also be available when submitted. Please note that no concentration of use data were provided indicating airbrush application. Nevertheless, no consumer habits and practices data or particle size data are publicly available to evaluate the exposure associated with this use type, thereby preempting the ability to evaluate risk or safety. Without information regarding the consumer habits and practices data or product particle size data (or other relevant particle data, e.g., diameter) related to this use technology, the data profile is incomplete, and the Panel is not able to determine safety for use in airbrush formulations. Accordingly, the data are insufficient to evaluate the exposure resulting from cosmetics applied via airbrush delivery systems.

According to the European Union, Oxyquinoline and Oxyquinoline Sulfate may be used as a stabilizer for hydrogen peroxide in rinse-off hair products at a maximum concentration of 0.3% (as base).[11] In addition, these ingredients may be used as a stabilizer for hydrogen peroxide in leave-on hair products at a maximum concentration of 0.03% (as base).

Non-Cosmetic

Oxyquinoline and Oxyquinoline Sulfate are used as reagents for detection of bismuth.[3] *These ingredients are also used as chelating agents in analysis of trace metals.*

The Code of Federal Regulations (CFR) indicate that Oxyquinoline is used as a topical over-the-counter (OTC) antifungal drug product (21CFR310.545) and Oxyquinoline Sulfate is used in OTC astringent drug products (21CFR310.545), as an active ingredient in OTC products in the treatment of boils (21CFR310.531), and as an active ingredient in pesticides (40CFR455). According to FDA's OTC ingredient list, in addition to the uses listed above, Oxyquinoline is used in oral health care products and Oxyquinoline Sulfate is used in skin protectants.[12] Oxyquinoline is also used in a prescription vaginal gel formulation, as a chelating agent in diagnostic radiopharmaceuticals, and has been studied for use in the treatment of certain diseases (e.g., AIDS, bacterial and fungal diseases, cancer).[12-15]

TOXICOKINETIC STUDIES

Oxyquinoline

Increased iron deposits were observed in tissues of rats orally administered Oxyquinoline (proportionate to the amount of iron available in the diet).[3] *Intravenous administration of Oxyquinoline resulted in the formation and excretion of glucuronide (found in bile and urine at concentration of 9 and 60% of the administered dose, respectively) and sulfate conjugates (observed in urine at concentration of up to 23% of the administered dose).*

Absorption, Distribution, Metabolism, and Excretion

Animal

Oral

Oxyquinoline

A single oral dose (method of oral administration not stated) of 10 mg/kg bw Oxyquinoline (details regarding radiolabeling not provided) was administered to rats (strain, sex, and number of animals not stated) to evaluate absorption and excretion.[5] The test substance was rapidly absorbed from the gastrointestinal tract. The majority of the radioactivity was eliminated by urine and feces by 8 h after administration. Administered radioactivity was excreted with a half-life of 28 min post-administration.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

An oral median lethal dose (LD_{50}) of 1200 mg/kg bw was established in an acute toxicity assay performed in rats.[3] *No signs of toxicity or irritancy were observed in an acute inhalation toxicity assay in which rats were exposed to aerosolized Oxyquinoline for 6 h. The intraperitoneal LD_{50} for Oxyquinoline was reported to be 48 mg/kg in mice, and the subcutaneous LD_{50} was reported to be 500 mg/animal in rats. The maximum practical dose in an acute percutaneous study in rats was determined to be > 4 ml/kg bw.*

In Vitro

Oxyquinoline Sulfate

An oral LD_{50} was estimated for Oxyquinoline Sulfate (up to 0.002 mg/ml) via a neutral red uptake assay using Balb 3T3 cells.[4] The LD_{50} was estimated to be 84.1 mg/kg bw.

Animal

Dermal

Oxyquinoline

A dermal LD_{50} of > 10,000 mg/kg bw was reported in an assay performed in rats given Oxyquinoline in water.[5,16] Animals were administered the test substance in water for 24 h, under occlusive conditions, and evaluated for 14 d.

Oxyquinoline Sulfate

A dermal LD_{50} of > 4000 mg/kg bw was reported in an assay using Oxyquinoline Sulfate in rats.[16] No other details were provided.

Oral

Oxyquinoline

The oral LD_{50} in mice and rats given Oxyquinoline (1% surfactant solution) was 177 mg/kg bw and 790 mg/kg bw (in females), respectively.[5,17] Oral LD_{50}s in mice, rats and guinea pigs given Oxyquinoline (concentration not stated) were reported to be 220 – 280 mg/kg bw, 1200 – 2300 mg/kg bw, and 1205 mg/kg bw, respectively.[18,19]

Oxyquinoline Sulfate

An oral LD_{50} in rats given Oxyquinoline Sulfate was reported to be 800 mg/kg bw (no details provided).[19] Oral LD_{50}s of 1200 – 2520 mg/kg bw in females and 2520 – 3180 mg/kg bw in males was determined in an acute oral toxicity assay performed in dogs given Oxyquinoline Sulfate.

Repeated-Dose Toxicity Studies

Oxyquinoline

In a 15-d study using mice (5/sex/group) given Oxyquinoline (0, 3000, 6000, 12,000, 25,000, or 50,000 ppm), all mice in the 25,000 and 50,000 ppm groups died.[3] Mice receiving 12,000 ppm Oxyquinoline lost weight and were emaciated. In another 15-d study performed in rats given the same test substance via diet, at the same concentrations, 3 male rats given 50,000 ppm and 1 male rat receiving 25,000 ppm died. Weight loss was observed in both sexes at the highest dose groups, compared to untreated controls. Lower mean body weight and increased liver and spleen weights (compared to controls) were observed in a study in which rats (9 males) were given a diet containing 0.8% Oxyquinoline for 16 wk, followed by a 10-wk period on a control diet.[3] Thirteen-wk studies were performed in mice (5/sex/group) and rats (5/sex/group) given Oxyquinoline (800, 1500, 3000, 6000, or 12,000 ppm) in the diet. Mean body weights were lower in all treated groups in male mice (compared to controls), and in female mice at the highest dose (compared to controls). In rats, lowered mean body weights were observed in males (at 12,000 ppm; compared to controls) and in females (at 6000 and 12,000 ppm; compared to controls). No compound-related lesions were observed in these studies.

Details regarding the repeated-dose toxicity studies summarized below are provided in Table 3.

A no-observable adverse effect level (NOAEL) of 1000 ppm was determined in a 14-d oral toxicity assay in which Wistar rats (5/sex/dose) were given Oxyquinoline at up to 8000 ppm via diet (decreased body weight gain and decreased food consumption observed at concentrations ≥ 3000 ppm).[17] An NOAEL of 200 mg/kg bw/d was determined in an assay in which Crj:CD rats (number of animals not stated) were treated with up to 400 mg/kg bw/d Oxyquinoline in methylcellulose solution via gavage (males treated for 42 d; females treated from 42 – 46 d).[5] Decreased food consumption, decreased body weight, abnormal blood chemistry, increased organ weights, and gastrointestinal abnormalities were observed at the highest dose level. Similarly, reduced food intake, reduced body weight, and abnormal blood parameters were observed in an assay in which Wistar rats (10/sex/dose) were given Oxyquinoline in the diet (at up to 6000 ppm) for 13 wk (adverse effects seen at concentrations ≥ 3000 ppm).[17] An NOAEL of > 100 mg/kg bw/d was determined in a 13-wk oral toxicity assay in which Oxyquinoline was given to Beagle dogs (4/sex/dose) at up to 100 mg/kg bw/d via capsules.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Details regarding the developmental and reproductive toxicity studies summarized below may be found in Table 4.

No adverse effects regarding evaluated developmental and reproductive toxicity parameters were observed in an assay in which Oxyquinoline in methylcellulose solution was given to Crj:CD rats (number of animals not stated) at doses up to 400 mg/kg bw/d (males treated for 42 d; females treated for 42 – 46 d (throughout mating and gestation)) via gavage.[5] Decreased fetal body weights (in mid- and high-dosed groups), decreased mean placental weights (at all doses), and skeletal malformations (at all doses) were observed in a prenatal developmental toxicity assay in which female Wistar rats (25/group) were given Oxyquinoline via corn oil (100, 300 and 600 mg/kg bw/d) on gestation days (GD) 6 -19 (gavage administration).[17] Adverse effects such as decreased body weights, decreased organ weighs, decreased live-born pup numbers, and developmental delays were observed in a 2-generation reproductive toxicity assay in which Wistar rats (26/sex/dose) were given up to 8000 mg/kg bw/d Oxyquinoline via the diet during mating, gestation, and lactation (adverse effects seen at concentrations ≥ 3000 ppm). A decreased number of live-born female pups (at 60 mg/kg bw/d) and skeletal malformations (at ≥ 15 mg/kg) were observed in a prenatal developmental toxicity assay in which female New Zealand white rabbits (25/dose) were given Oxyquinoline in corn oil, via gavage, on GD 6 – 28, at up to 60 mg/kg bw/d.

GENOTOXICITY STUDIES

Oxyquinoline

Oxyquinoline was mutagenic in the presence of metabolic activation in numerous Ames tests (only in Salmonella typhimurium strain TA100 at 100 µg/ plate in one study and 600 µg/plate in another; in two strains tested (details not provided); in TA98 and TA100 (only strains that were tested) at 200 µg/plate; only in TA98 and TA100 at 125 µg/ml; in all strains tested in one study (details not provided)).[3] *Oxyquinoline, however, was not mutagenic in Ames tests when evaluated without metabolic activation. Oxyquinoline (concentration not reported) was also mutagenic in a L5178Y tk^+/tk^- mouse lymphoma cell forward mutation assay and caused increases (at 40 - 70 µM) in chromosomal aberrations in Chinese hamster ovary cells.* [3]

Oxyquinoline did not induce unscheduled DNA synthesis or mitogenesis in hepatocytes of male rats that were given up to 225 mg/kg (method of administration not stated) for 24 h. In a different assay, Oxyquinoline was slightly active in inducing unscheduled DNA synthesis and did not cause DNA fragmentation (no details provided). In an in vivo–in vitro hepatocyte replicative DNA synthesis test, Oxyquinoline (125 and 250 mg/kg) failed to induce replicative DNA synthesis in hepatocytes (no other details provided). In vivo, Oxyquinoline (single or 28 repeated doses of 500 mg/kg) did not result in chromosomal aberrations or replicative DNA synthesis in the liver of treated rats. Oxyquinoline was not genotoxic in a bone marrow micronucleus assay in mice (0.4 ml of up to 43 mg/kg via intraperitoneal injection for 3 d), and results were also negative in another in vivo micronucleus test (details not provided).

Oxyquinoline Sulfate

Oxyquinoline Sulfate (500 µg/plate) was determined to be mutagenic when evaluated in S. typhimurium strains TA98 and TA100 (but not other strains) when evaluated with metabolic activation. Mutagenicity was not observed without metabolic activation.

Details regarding the genotoxicity studies summarized below may be found in Table 5.

A 2-part Ames assay using Oxyquinoline at up to 1000 µg/plate in *S. typhimurium* strains yielded negative results (performed with and without metabolic activation).[5] Conversely, Oxyquinoline was genotoxic in *S. typhimurium* strains TA97 and TA100 when evaluation with metabolic activation (tested at up to 100 µg/plate; non-genotoxic without metabolic activation.[17] Clastogenicity was observed in cells exposed to 125 µg/ml without metabolic activation and in cells exposed to ≥ 4 µg/ml with metabolic activation in a chromosomal aberration assay performed using Oxyquinoline on Chinese hamster V79 cells. Oxyquinoline Sulfate (up to 666 µg/plate) was non-genotoxic in *S. typhimurium* strains TA98 and TA100 without metabolic activation, and genotoxic in these strains when evaluated with metabolic activation.[20] No transformation of cells was observed in a cell transformation assay performed on BALB/c-3T3 cells using Oxyquinoline Sulfate at up to 0.5 µg/ml. [4] Oxyquinoline Sulfate (up to 5.3 µg/ml) was considered to be clastogenic in a human lymphocytes assay. In vivo assays (chromosomal aberration assays (up to 300 mg/kg bw), sister chromatid exchange assay (up to 100 mg/kg bw), unscheduled DNA synthesis assay (up to 500 mg/kg bw), erythrocyte micronucleus assay (up to 35 mg/kg bw)) performed on Oxyquinoline yielded predominantly negative results.[17] However, Oxyquinoline (up to 100 mg/kg bw; intraperitoneal injection) was determined to be genotoxic when evaluated in male CD-1 mice (number of animals not stated) in an erythrocyte micronucleus assay.

CARCINOGENICITY STUDIES

Oxyquinoline

Oxyquinoline given topically (at 225 mg/kg, 5x/wk) or in the diet (at 3000 ppm for 24 wk) did not increase the incidence of neoplasms in mice (number of animals not stated).[3] *No rapid tumor response was observed in an assay in which transgenic mice (mice carrying the human prototype c-Ha-ras gene as a model for rapid carcinogenicity testing) were fed Oxyquinoline (up to 3000 ppm) for 24 wk. No compound-related lesions were observed in an assay in which male rats (15/group) were fed diets containing 0.8% Oxyquinoline for 52 or 78 wk. Oxyquinoline was considered to be non-carcinogenic in an assay in which male and female rats (30/group) were given 0.1% Oxyquinoline in the diet for 104 wk. No compound-related lesions were observed in 2-yr assays performed in mice (50/sex/group) and rats (50/sex/group) given 0.15 or 0.3% Oxyquinoline in the diet. Oxyquinoline was not considered to be a carcinogen in an assay in which 20 female mice were given twice weekly intravaginal doses of 1% Oxyquinoline in gum traganth (total of 100 treatments). No carcinogenicity was observed in an assay in which Oxyquinoline (12.5% in cholesterol or 20% in paraffin wax) was implanted in the urinary bladders of mice (number of animals not stated). Studies performed using genetically altered mice, in one case carrying the human c-Ha-ras gene, suggested that Oxyquinoline was not carcinogenic.*

ANTI-CARCINOGENICITY STUDIES

Oxyquinoline

The effect of Oxyquinoline (5, 10, 50, 100 and 500 µM) on human lung cancer A549 cells was evaluated in vitro.[21] The apoptotic and caspase-mediated pathways were evaluated. The cytotoxic activity of Oxyquinoline on A549 cells, evaluated as IC_{50} values, were 26, 5, and 7.2 µM at 24, 48, and 72 h, respectively. Results also indicated that Oxyquinoline significantly inhibited A549 cells and activated the intrinsic pathways of apoptosis. In addition, expressions of tumor protein P53, B cell lymphoma 2,

and signal transducer and activator of transcription 3 were inhibited in A549 cell lines, confirming the metastasis inhibitory potential of Oxyquinoline.

OTHER RELEVANT STUDIES

DNA Binding

Oxyquinoline

In one assay, it was apparent that Oxyquinoline binds to DNA in the presence of liver extract.[3] No other details were provided.

DERMAL IRRITATION AND SENSITIZATION STUDIES

Oxyquinoline was considered to be a moderate irritant (primary irritation index score of 2.8) in a dermal irritation assay in which an aqueous preparation of Oxyquinoline was painted on the skin of 6 rabbits (no other details provided).[3] In a different assay, Oxyquinoline (0.5 g solid) was applied under occlusive patches to intact and scarified rabbit skin for 24 h. The test substance was considered to be mildly irritating. A human repeat insult patch test (HRIPT) was performed on 193 subjects over a 6-wk period. Oxyquinoline (1% in petrolatum; 0.2 g) was applied under occlusive patches for 24 h for each induction and challenge application. The test substance was considered to be non-sensitizing.

Irritation

In Silico

Oxyquinoline Sulfate

The irritation potential of Oxyquinoline Sulfate was evaluated using a QSAR model (UL REACHAcross™ v.3.1.4).[4] This ingredient was not predicted to be irritating.

Animal

Oxyquinoline

Oxyquinoline (concentration and vehicle not stated; 0.5 g) was considered to be non-irritating in an assay performed in New Zealand White rabbits (n = 8). Applications were made on intact and scarified skin, under occlusive conditions, for 24 h.[17] Similarly, Oxyquinoline (tested at 100%; no vehicle 0.5 g) was considered to be non-irritating in a dermal irritation assay performed according to Organisation for Economic Cooperation and Development (OECD) test guidelines (TG) 404. This assay was performed using 3 female New Zealand white rabbits, under semi-occlusive conditions (4-h exposures).[5]

Sensitization

In Chemico

Oxyquinoline Sulfate

A direct peptide reactivity assay (DPRA) was performed according to OECD TG 442C using Oxyquinoline Sulfate (concentration and vehicle not stated; negative control: phosphate buffer and water; positive control: cinnamic aldehyde).[4] The test substance was considered to be a sensitizer due to measurable cysteine-peptide depletion (cysteine-peptide depletion: 39.88; lysine-peptide depletion: 0.49). Controls gave expected results.

Human

Oxyquinoline Sulfate

A 3-series sensitization assay was performed by patch testing subjects during various time periods (first test series (1967 – 1968): 127 subjects; second test series (1969): 100 subjects; third test series (1969): 100 subjects).[17]Sensitization rates in series 1, 2, and 3 were reported to be 4.7, 8, and 6%, respectively. No other details were provided for this study.

OCULAR IRRITATION STUDIES

Oxyquinoline

In an ocular irritation assay, Oxyquinoline (100 mg) was placed in the conjunctival sac of 6 rabbits. The test substance was considered to be an ocular irritant. In a different ocular irritation assay performed in rabbits, Oxyquinoline (100 mg) was considered to be slightly irritating.

Details regarding the ocular irritation studies summarized below may be found in Table 6.

An ocular irritation score of 134 was determined in an in vitro bovine corneal opacity and permeability assay using 20% Oxyquinoline Sulfate in saline (scores > 55 indicate serious eye damage).[4] Oxyquinoline (no vehicle; tested neat) was considered to be irritating when applied to the eyes of 3 rabbits.[5] Conversely, 10% Oxyquinoline (vehicle not stated) was determined to be non-irritating in an ocular irritation assay performed in 8 rabbits.[17]

CLINICAL STUDIES

Retrospective and Multicenter Studies

Oxyquinoline

An epidermal test series was performed in 450 subjects for determination of contact eczema caused by drugs within a 6-yr period (no other study details provided).[17] Hypersensitivity to Oxyquinoline was observed in 3 patients. Oxyquinoline was determined to be a weak sensitizer.

Case Reports

Oxyquinoline and Oxyquinoline Sulfate

A 32-yr-old subject (sex not stated) with dermatitis was treated with a 0.1% aqueous solution of Oxyquinoline and an ointment containing 0.02% Oxyquinoline.[17] Eczema was exacerbated upon treatment. Epidermal patch tests with an aqueous solution of Oxyquinoline Sulfate yielded positive skin reactions and inflammation. A clear reaction of infiltration was observed at concentrations above 0.01%. No other details were provided.

SUMMARY

Oxyquinoline and Oxyquinoline Sulfate are reported to function in cosmetics as chelating agents and cosmetic biocides. These ingredients were first reviewed by the Panel in a safety assessment published in 1992. At that time, the Panel concluded that the data were insufficient to support a conclusion of safety for these ingredients. In 2006, the Panel published a Final Amended Report on these ingredients, with the conclusion that Oxyquinoline and Oxyquinoline Sulfate are safe as used as stabilizers for hydrogen peroxide in rinse-off products, and that the data is insufficient to support the safety of Oxyquinoline and Oxyquinoline Sulfate in leave-on cosmetic products. In 2024, the Panel determined that this safety assessment should be re-opened for the evaluation of new data and to correct the conclusion from the 2006 report (2006 report contains typographical error in conclusion).

In 2002, Oxyquinoline and Oxyquinoline Sulfate were reported to be used at up to 0.1% in 4 and 7 formulations, respectively. FDA VCRP (2023) and 2023 concentration of use data indicate use of Oxyquinoline and Oxyquinoline Sulfate in 1 formulation (no concentrations of use reported), and 19 formulations (at up to 0.15%), respectively. RLD indicate that Oxyquinoline and Oxyquinoline Sulfate are used in 11 and 575 total formulations, respectively.

Oxyquinoline was rapidly absorbed by the gastrointestinal tract when evaluated in a rats. In this assay, rats were given a single oral dose of 10 mg/kg bw Oxyquinoline.

An oral LD_{50} of 84.1 mg/kg bw was estimated in a neutral red uptake assay using Oxyquinoline Sulfate (up to 0.002 mg/ml). A dermal LD_{50} of > 10,000 mg/kg bw was reported in an assay performed in rats (occlusive conditions). A dermal LD_{50} of > 4000 mg/kg bw was reported in an assay using Oxyquinoline Sulfate. Oral LD_{50}s in mice and rats given Oxyquinoline (1% surfactant solution) were reported to be 177 mg/kg bw and 790 mg/kg bw, respectively. Oral LD_{50}s in mice, rats and guinea pigs given Oxyquinoline were reported to be 220 – 280 mg/kg bw, 1200 – 2300 mg/kg bw, and 1205 mg/kg bw, respectively. Oral LD_{50}s for Oxyquinoline Sulfate in rats, female dogs, and male dogs were reported to be 800, 1200 – 2520, and 2520 – 3180 mg/kg bw, respectively.

An NOAEL of 1000 ppm was determined in a 14-d oral toxicity assay in which Wistar rats were given Oxyquinoline at up to 8000 ppm via diet. A NOAEL of 200 mg/kg bw/d was determined in an assay in which Crj:CD rats were treated with up to 400 mg/kg bw/d Oxyquinoline in methylcellulose solution via gavage (males treated for 42 d; females treated from 42 – 46 d). Reduced food intake, reduced body weight, and abnormal blood parameters were observed in an assay in which Wistar rats were given Oxyquinoline in the diet (at up to 6000 ppm) for 13 wks (adverse effects seen at concentrations ≥ 3000 ppm). A NOAEL of > 100 mg/kg bw/d was determined in a 13-wk oral toxicity assay in which Oxyquinoline was given to Beagle dogs at up to 100 mg/kg bw/d via capsules.

No adverse effects regarding evaluated developmental and reproductive toxicity parameters were observed in an assay in which Oxyquinoline in methylcellulose solution was given to Crj:CD rats at concentrations of up to 400 mg/kg bw/d (males treated for 42 d; females treated for 42 – 46 d (throughout mating and gestation); treatment via gavage). Decreased fetal body weights (in mid- and high-dosed groups), decreased mean placental weights (at all doses), and skeletal malformations (at all doses) were observed in a prenatal developmental toxicity assay in which female Wistar rats were given Oxyquinoline via corn oil (up to 600 mg/kg bw/d) on GD 6 -19 (gavage administration). Adverse effects such as decreased body weights, decreased organ weighs, decreased live-born pup numbers, and developmental delays were observed in a 2-generation reproductive toxicity assay in which Wistar rats were given up to 8000 mg/kg bw/d Oxyquinoline via the diet during mating, gestation, and lactation (adverse effects seen at concentrations ≥ 3000 ppm). A decreased number of live-born female pups (at 60 mg/kg bw/d) and skeletal malformations (at ≥ 15 mg/kg) were observed in a prenatal developmental toxicity assay in which female New Zealand white rabbits were given Oxyquinoline in corn oil, via gavage, on GD 6 – 28, at up to 60 mg/kg bw/d.

In vitro genotoxicity assays (Ames assays, chromosomal aberration assay, cell transformation assay, human lymphocytes assay) performed using Oxyquinoline and Oxyquinoline Sulfate yielded mixed results. However, in vivo assays (chromosomal aberration assays, sister chromatid exchange assay, unscheduled DNA synthesis assay, erythrocyte micronucleus assay) performed

on Oxyquinoline yielded predominantly negative results. Oxyquinoline (up to 100 mg/kg bw; intraperitoneal injection) was determined to be genotoxic when evaluated in male mice in an erythrocyte micronucleus assay.

Oxyquinoline (up to 500 µM) resulted in cytotoxicity in A549 cells when evaluated in vitro. Results of this study also indicated that Oxyquinoline activated the intrinsic pathways of apoptosis, and inhibited expressions of tumor protein P53, B cell lymphoma 2, and signal transducer and activator of transcription 3.

Oxyquinoline Sulfate was not predicted to be irritating according to a QSAR analysis. Oxyquinoline (concentration not stated) was not determined to be non-irritating in an assay performed in rabbits, on intact and scarified sites, under occlusive conditions (24-h application) and in an assay in which Oxyquinoline (tested neat) was applied under semi-occlusive conditions (4-h application) to the skin of rabbits. Oxyquinoline Sulfate (concentration not stated) was considered to be a sensitizer in a DPRA. A 3-series sensitization assay was performed by patch testing subjects during various time periods (first test series (1967 – 1968); second test series (1969); third test series (1969)). Sensitization rates in series 1, 2, and 3 were reported to be 4.7, 8, and 6%, respectively.

Oxyquinoline Sulfate (20% in saline) was determined to induce serious eye damage in an in vitro bovine corneal opacity assay. Oxyquinoline (tested neat) was considered to be irritating to rabbit eyes. Conversely, 10% Oxyquinoline was determined to be non-irritating in rabbit eyes.

Oxyquinoline was determined to be a weak sensitizer in an epidermal test series performed in 450 subjects. Subjects were analyzed for contact eczema caused by drugs within a 6-yr period.

A 32-yr-old subject with dermatitis experienced exacerbated eczema following treatment with formulations containing 0.1 and 0.2% Oxyquinoline. Epidermal patch tests using an aqueous solution of Oxyquinoline Sulfate yielded positive skin reactions.

PREVIOUS DISCUSSION

Discussion from Original Report Published in 1992

The Expert Panel notes that Oxyquinoline is an active cosmetic ingredient that binds DNA and is mutagenic in some assay systems. The CIR Expert Panel concurs with the Environmental Protection Agency that bacterial mutagenic assay systems are not appropriate for assessing the mutagenic potential of microbiocides in mammalian systems. However, the Expert Panel did not consider the available negative oral carcinogenic assays were sufficient to evaluate the safety of use of Oxyquinoline in humans who are exposed to this ingredient in cosmetic products applied to the skin. Therefore, a skin carcinogenicity study in one animal species is needed. Human skin irritation and sensitization (including photosensitization) data are also needed before a conclusion on the safety of use of Oxyquinoline and Oxyquinoline Sulfate in cosmetic products can be made.

Section 1, paragraph (p) of CIR Procedures states that "A lack of information about an ingredient shall not be sufficient to justify a determination of safety." In accordance with Section 30(j)(2)(A) of the CIR procedures, the Panel informed the public of its decision that the data on Oxyquinoline and Oxyquinoline Sulfate are insufficient to determine whether these ingredients, under each relevant condition of use, are either safe or unsafe. The Panel released a Notice of Insufficient Data Announcement on November 12, 1990 outlining the data needed to assess the safety of Oxyquinoline and Oxyquinoline Sulfate. The types of data required included: (a) dermal carcinogenesis (mouse) data, if (a) is negative, (b) skin irritation (human), (c) skin sensitization and photosensitization (human).

No offer to supply results from a dermal carcinogenicity study was received. In accordance with Section 45 of CIR Procedures, the Expert Panel will issue a Final Safety Evaluation Report – Insufficient Data. When the requested new data become available, the Panel will reconsider the Final Report in accordance with Section 46 of the CIR Procedures, Amendment of a Final Report.

Discussion from Amended Report Published in 2006

In its earlier safety assessment of these ingredients, the CIR Expert Panel had concluded that the available data were insufficient to support their safety in cosmetics. The Expert Panel notes that Oxyquinoline binds to DNA and is mutagenic in some assay systems. The CIR Expert Panel concurs with the position of the Environmental Protection Agency that bacterial mutagenic assay systems are not appropriate for the assessing the mutagenic potential of microbiocides in mammalian systems. The prevalence of data from mammalian genotoxicity test systems indicates no genotoxicity. In addition, animal carcinogenicity tests have uniformly been negative. Recent use of genetically-altered mice in tests to evaluate carcinogenicity have found that Oxyquinoline is not carcinogenic. Although the Panel recognizes that the International Agency for Research on Cancer stated in 1987 that the available data were inadequate to determine the carcinogenicity of Oxyquinoline in animals, the data now appear sufficient to determine that Oxyquinoline is not a carcinogen in test animals.

The available clinical data demonstrate that Oxyquinoline is neither an irritant nor a sensitizer when tested at 1% in petrolatum.

The Panel was concerned with the absence of impurities data and information on the extent of skin penetration or its surrogate, the octanol/water partition coefficient. Oxyquinoline is virtually insoluble in water, suggesting that the skin penetration is unlikely. Oxyquinoline Sulfate, however, is soluble in water and information as to its skin penetration is lacking. To some extent, the absence of any carcinogenic effect when Oxyquinoline was applied topically to mice is reassuring. This finding,

however, does not rule out systemic effects of absorbed Oxyquinoline Sulfate. During the discussion, it was emphasized that the likely intended use of this ingredient in cosmetics is as a stabilizer for hydrogen peroxide in hair care cosmetic products. Even if there were skin absorption, given the safety test data that are available for Oxyquinoline, it is unlikely that there would be any systemic toxicity from such low concentrations in hydrogen peroxide containing hair care cosmetic products.

The Panel recognizes that use as a stabilizer in for hydrogen peroxide in hair care cosmetic products is approved by use in the European Union for leave-on products at ≤ 0.03% and for rinse-offs at ≤ 0.3%, but was not clear regarding the basis for that finding. The available data demonstrating the absence of irritation and sensitization at concentrations up to 1% and the use of these ingredients at concentrations of 1% or less in rinse-off hair care cosmetic products supports the safety of these ingredients as a stabilizer for hydrogen peroxide in hair cosmetic products. The Panel concluded that Oxyquinoline and Oxyquinoline Sulfate in rinse-off hair care products are safe in the present practices of use.

For leave-on cosmetic products, however, the Panel did not believe there were sufficient data. The data needed in order to complete the safety assessment of Oxyquinoline and Oxyquinoline Sulfate in leave-on cosmetic products are (1) UV absorption data - if significant absorption occurs, then photoirritation/photosensitization data will be needed; and (2) impurities data.

DISCUSSION

To be determined.

CONCLUSION

To be determined.

TABLES

Table 1. Chemical properties

Property	Value	Reference
	Oxyquinoline	
Physical Form	powder or crystals	3
Color	white	3
Odor	phenolic odor	6
Molecular Weight (g/mol)	145.2	3
Specific Gravity (@ 20 ºC)	1.03	3
Vapor pressure (mmHg@ 25 ºC)	0.0016	6
Melting Point (ºC)	76	3
Boiling Point (ºC)	267	3
Water Solubility	virtually insoluble	3
log K_{ow}	2.02	6
Disassociation constants (pKa) (@ 20ºC)	5.02	3
	Oxyquinoline Sulfate	
Physical Form	crystalline powder	3
Color	pale yellow	3
Odor	saffron odor	3
Molecular Weight (g/mol)	243	3
Melting Point (ºC)	175 - 178	3
Water Solubility	freely soluble	3

Table 2. Frequency and concentration of use according to likely duration and exposure and by product category

	Oxyquinoline					Oxyquinoline Sulfate				
	# of Uses			*Max Conc of Use*		*# of Uses*			*Max Conc of Use*	
	RLD (2024)[9]	**VCRP (2023)[8]**	**VCRP (2002)[3]**	**% (2023)[10]**	**% (2002)[3]**	**RLD (2024)[9]**	**VCRP (2023)[8]**	**VCRP (2002)[3]**	**% (2023)[10]**	**% (2002)[3]**
Totals*	**11**	**1**	**4**	**NR**	**0.1**	**575**	**19**	**7**	**0.0067 – 0.15**	**0.01 – 0.1**
summarized by likely duration and exposure**										
Duration of Use										
Leave-On	***	*NR*	*4*	*NR*	*0.1*	***	*3*	*3*	*0.15*	*0.05*
Rinse-Off	***	*1*	*NR*	*NR*	*0.1*	***	*16*	*4*	*0.0067 – 0.05*	*0.05 – 0.1*
Diluted for (Bath) Use	***	*NR*	*NR*	*NR*	*NR*	***	*NR*	*NR*	*NR*	*NR*
Exposure Type										
Eye Area	***	NR	NR	NR	NR	***	NR	NR	NR	NR
Incidental Ingestion	***	NR	NR	NR	NR	***	2	NR	NR	NR
Incidental Inhalation-Spray	***	NR	1[a]	NR	NR	***	NR	1[a]; 2[b]	NR	NR
Incidental Inhalation-Powder	***	NR	NR	NR	0.1	***	NR	2[b]	NR	0.05
Dermal Contact	***	NR	2	NR	0.1	***	NR	2	NR	0.05
Deodorant (underarm)	***	NR	NR	NR	NR	***	NR	NR	NR	NR
Hair - Non-Coloring	***	NR	2	NR	0.1	***	1	3	0.0067 – 0.15	0.01 – 0.1
Hair-Coloring	***	1	NR	NR	NR	***	16	2	0.015 – 0.05	0.05
Nail	***	NR	NR	NR	NR	***	NR	NR	NR	NR
Mucous Membrane	***	NR	NR	NR	NR	***	2	NR	NR	NR
Baby Products	***	NR	NR	NR	NR	***	NR	NR	NR	NR
as reported by product category										
Eye Makeup Preparations (not children's)						***2***				
Eyelash and Eyebrow Preparations (primers, conditioners, serums, fortifiers)	NR	NA	NA	NA	NA	2	NA	NA	NA	NA
Fragrance Preparations	***3***									
Powders (dusting/talcum, excl aftershave talc)	NR	NR	NR	NR	0.1	NR	NR	NR	NR	0.05
Other Fragrance Preparations	3	NR	NR	NR	NR	NR	NR	NR	NR	NR
Hair Preparations (non-coloring)						***55***				
Hair Conditioners	NR	NR	NR	NR	NR	1 (r.o.)	NR	NR	NR	NR
Hair Straighteners	NR	NR	NR	NR	NR	NR	NR	NR	NR	0.01
Permanent Waves	NR	NR	NR	NR	NR	7	NR	2	0.0067	0.01
Rinses (non-coloring)	NR	NR	NR	NR	0.1	3	NR	NR	NR	0.1
Shampoos (non-coloring)	NR	NR	NR	NR	NR	3 (r.o.)	NR	NR	NR	NR
Tonics, Dressings, and Other Hair Grooming Aids	NR	NR	1	NR	NR	NR	NR	1	NR	NR
Wave Sets	NR	NR	NR	NR	NR	1	NR	NR	NR	NR
Other Hair Preparations	NR	NR	1	NR	NR	1 (l.o.); 42 (r.o.)	1	NR	0.15	NR
Hair Coloring Preparations	***11***					***521***				
Hair Dyes and Colors (all types requiring caution statements and patch tests)	3	NR	NR	NR	NR	212	NR	1	0.015 – 0.05	0.05
Hair Tints	2	1	NR	NR	NR	18	NR	NR	NR	NR
Hair Rinses	3 (r.o.)	NR	NR	NR	NR	9 (r.o.)	NR	NR	NR	NR
Hair Shampoos (coloring)	5 (r.o.)	NR	NR	NR	NR	7 (r.o.)	4	NR	NR	NR
Hair Lighteners with Color	NR	NR	NR	NR	NR	8	NR	NR	NR	NR
Hair Bleaches	NR	NR	NR	NR	NR	59	4	NR	0.015	0.05
Other Hair Coloring Preparation	3 (r.o.)	NR	NR	NR	NR	8 (l.o.); 246 (r.o.)	8	1	NR	NR
Makeup Preparations (not eye; not children's)										
Lipstick and Lip Glosses	NR	NR	NR	NR	NR	NR	2	NR	NR	NR
Shaving Preparations						***1***				
Other Shaving Preparation Products	NR	NR	NR	NR	NR	1	NR	NR	NR	NR

Table 2. Frequency and concentration of use according to likely duration and exposure and by product category

	Oxyquinoline					Oxyquinoline Sulfate				
	# of Uses			*Max Conc of Use*		*# of Uses*			*Max Conc of Use*	
	RLD (2024)[9]	**VCRP (2023)[8]**	**VCRP (2002)[3]**	**% (2023)[10]**	**% (2002)[3]**	**RLD (2024)[9]**	**VCRP (2023)[8]**	**VCRP (2002)[3]**	**% (2023)[10]**	**% (2002)[3]**
Skin Care Preparations						***1***				
Face and neck (excluding shaving preparations)	NR	NR	NR	NR	NR	1 (r.o.)	NR	NR	NR	NR
Body and Hand (excluding shaving preparations)	NR	NR	NR	NR	NR	NR	NR	2	NR	NR
Other Skin Care Preparations	NR	NR	2	NR	NR	NR	NR	NR	NR	NR

NR – not reported; NA – not applicable (this category was not part of the VCRP)

l.o. – leave-on; r.o. – rinse-off

*The total FOU provided for RLD refers to the ingredient count supplied by FDA, and is not a summation of the number of uses per category because each product may be categorized under multiple product categories. For data supplied via the VCRP or by the Council survey, the sum of all exposure types may not equal the sum of total uses because each ingredient may be used in cosmetics with multiple exposure types.

**Likely duration and exposure are derived from VCRP and survey data based on product category (see Use Categorization https://www.cir-safety.org/cir-findings)

***Because RLD are product-centric and not ingredient-centric, each ingredient may be reported under several product categories, making a summation of RLD misleading in comparison to VCRP data. Accordingly, RLD are presented below by product category (as supplied by FDA), but are not summarized by likely duration and exposure.

****at the time of the 2006 safety assessment, concentration of use data were not reported by the FDA, and a concentration of use survey was not conducted; 2002 data were presented in the original assessment and are reported here

[a] It is possible these products are sprays, but it is not specified whether the reported uses are sprays.

[b] Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, therefore the information is captured in both categories

Table 3. Oral repeated dose toxicity studies

Test Article	Vehicle	Animals/Group	Study Duration	Dose/Concentration	Protocol	Results	Reference
Oxyquinoline	NR	Wistar rats (5/sex/dose)	14 d	0, 1000, 3000, and 8000 ppm	OECD TG 407; range-finding study; rats given test substance via diet; rats observed for mortality, toxicity, body weight changes, hematology, clotting and clinical chemistry	decreased body weight gain in both sexes and decreased food consumption in males observed at 3000 and 8000 ppm; no other adverse effects were observed; the NOAEL was determined to be 1000 ppm.	17
Oxyquinoline	methylcellulose solution	Crj:CD rats (male and females; number of animals not stated)	42 – 46 d	0, 100, 200, and 400 mg/kg bw/d	OECD TG 422; gavage administration; males treated for 42 d; females treated from 42-46 d (from 14 d before mating to day 4 of lactation)	NOAEL of 200 mg/kg bw/d in male and female rats; adverse effects observed at the 400 mg/kg bw/d dose level include decrease in food consumption and body weight, abnormal blood chemistry (e.g., decreased liver enzymes), increased liver and kidney weights, and gastrointestinal abnormalities	5
Oxyquinoline	diet	Wistar rats (10/sex/dose)	13 wk	principal group: 0, 1000, 3000, or 6000 ppm satellite group: 0 or 6000 ppm	OECD TG 408; rats treated via diet; satellite group evaluated for 4 wk after exposure period	reduced food intake in males and females at highest dose; reduced body weight in males at highest dose; reduced red blood cell count and hematocrit in females and increased mean corpuscular volume in males at concentrations ≥ 3000 ppm	17
Oxyquinoline	NR	Beagle dogs (4/sex/dose)	13 wk	0, 10, 50 or 100 mg/kg bw/d	OECD TG 409; treatment administered via capsules	statistically significant decrease in food consumption observed in females at doses ≥ 50 mg/kg bw/d; an increase in the relative weight of the right thyroid gland at 50 mg/kg bw/d and the left thyroid gland at 1000 mg/kg bw/d was observed in males (however; these values fell into the range of historical controls data); other adverse effects not observed; NOAEL determined to be > 100 mg/kg bw/d	17

NOAEL = no-observable-adverse-effect-level; OECD = Organisation for Economic Co-operation and Development; TG = test guidelines

Table 4. Developmental and reproductive toxicity studies

Test Article	Vehicle	Animals/Group	Dose/Concentration	Procedure	Results	Reference
Oxyquinoline	methylcellulose solution	Crj:CD rats (male and females; number of animals not stated)	0, 100, 200, and 400 mg/kg bw/d	OECD TG 422; males treated for 42 d; females treated from 42 - 46 d (from 14 d before mating to day 4 of lactation); gavage administration; maternal parameters and F1 generation evaluated	no adverse effect on reproductive parameters/ development were observed; NOAEL for reproductive and developmental toxicity determined to be 400 mg/kg bw/d	5
Oxyquinoline	corn oil	female Wistar rats (25/group)	0, 100, 300, or 600 mg/kg bw/d	OECD TG 414; prenatal developmental toxicity study; gavage administration on GD 6 – 19	decreased maternal body weights observed at 2 highest dose levels; no effects on reproductive parameters (number of live fetuses, resorptions, implantation losses, corpora lutea, and litter numbers); decreased fetal body weight at 300 and 600 mg/kg bw/d; mean placental weight decreased at all test concentrations; skeletal malformations observed in fetuses of all doses (decreased number of fetal ossification centers and increased incidence of skeletal retardations); increased incidence of visceral variations at ≥ 300 mg/kg bw/d	17
Oxyquinoline	diet	Wistar rats (26/sex/dose)	0, 1000, 3000, or 8000 mg/kg bw/d	OECD TG 416; 2-generation reproductive toxicity study; animals exposed during mating, gestation, and lactation via diet	decreased body weight observed in F0 and F1 parents at ≥ 3000 ppm; food intake was decreased in F0 and F1 parents at 8000 ppm; in F0 animals, ovary, kidney, and adrenal weights were reduced in females at 8000 ppm; prostate and spleen weight reduced in males at ≥ 3000 ppm; decreased kidney, brain, and adrenal weights observed in F1 animals at 8000 ppm; in F1 animals exposed at 3000 ppm, seminal vesicle and adrenal weights were reduced in males, and ovary weight was reduced in females; statistically-significant decrease in live-born pup numbers observed in F0 animals at 8000 ppm compared to controls; in F1 animals, at 8000 ppm, numbers of complete estrous cycles were reduced, length of estrous cycle increased, and a statistically significant decrease in live born pup numbers was observed compared to controls; decreased body weight, developmental delays observed in F1 and F2 pups at 8000 ppm; organ weights reduced in F1 and F2 pups at ≥ 3000 ppm	17
Oxyquinoline	corn oil	female New Zealand white rabbits (25/dose)	0, 5, 15, or 60 mg/kg bw/d	OECD TG 414; prenatal developmental toxicity study; animals dosed via gavage on GD 6 – 28	at 60 mg/kg bw/d, a decreased number of live-born female pups and increased pre-implantation loss was observed (pre-implantation loss was not reported to be treatment-related as dosing commenced on GD 6 - at which point implantation is already to have occurred); skeletal malformations observed in fetuses of all doses; significantly decreased numbers of fetal ossification centers in sternebrae, and increased incidence of head (soft tissue) variations and incidence of rare omphalocele malformation observed at ≥ 15 mg/kg bw/d; maternal toxicity observed in some rabbits of the 15 mg/kg bw/d group; however, teratogenic effects observed in all cases without maternal toxicity	17

GD = gestation days; OECD = Organisation for Economic Co-operation and Development; TG = test guidelines

Table 5. Genotoxicity studies

Test Article	Vehicle	Concentration/Dose	Test System	Protocol	Results	Reference
IN VITRO						
Oxyquinoline	DMSO	Experiment I: 1.0, 3.16, 10.0, 31.6, 100, 316 and 1000 µg/plate with and without metabolic activation Experiment II: 0.5, 1.58, 5.0, 15.8, 50, 158 and 500 µg/plate with and without metabolic activation	*S typhimurium* strains TA1535, TA1537, TA98, TA100 and TA 102	OECD TG 471; 2-part Ames assay performed with and without metabolic activation; negative control: DMSO; positive controls: sodium azide, methyl methane sulfonate, 4-nitro-*o*-phenylenediamine; 2 aminoanthracene	non-genotoxic; controls gave expected results	5
Oxyquinoline	NR	0, 1, 3, 10, 16, 33, 66, and 100 µg/ plate	*S. typhimurium* strains TA97, TA98, TA100, and TA1535	Ames assay performed with and without metabolic activation	genotoxic in TA97 and TA100 with metabolic activation; non-genotoxic in TA97 and TA100 without metabolic activation; non-genotoxic in TA98 and TA1535 with and without metabolic activation	17
Oxyquinoline	NR	without metabolic activation: 31.3, 62.5, and 125 µg/ml with metabolic activation: 2, 4, 5, 6.5, and 8 µg/ml	Chinese hamster V79 cells	OECD TG 473; chromosomal aberration assay performed with and without metabolic activation; 4 h exposure period; 20 h fixation period	clastogenicity observed in cells exposed to 125 µg/ml without metabolic activation in cells exposed to ≥ 4 µg/ml with metabolic activation	17
Oxyquinoline Sulfate	water	1, 3, 10, 16, 33, 100, 166, 333, and 666 µg/plate	*S. typhimurium* strains TA98 and TA100	Ames assay performed with and without metabolic activation; negative control: water; positive controls: 2-aminoanthracene, sodium azide, 4-nitro-o-phenylenediamine	non-genotoxic in both strains without metabolic activation; genotoxic in both strains with metabolic activation; controls gave expected results	20
Oxyquinoline Sulfate	NR	0.031, 0.063, 0.125, 0.250 or 0.500 µg/ml	BALB/c-3T3 cells	Cell transformation assay; 72-h exposure	no transformation of cells observed	4
Oxyquinoline Sulfate	NR	2.6 – 5.3 µg/ml (individual doses not provided)	human lymphocytes	human lymphocytes assay	clastogenic	4
IN VIVO						
Oxyquinoline	NR	75, 150, and 300 mg/kg bw	male NMRI mice (number of animals not stated) spermatagonial cells	OECD TG 483; chromosomal aberration assay; single oral dose by gavage; sampling times: 24 and 48 h	non-genotoxic	17
Oxyquinoline	NR	17-h exposure time: 0, 25, 50, and 100 mg/kg bw 36-h exposure time: 0, 17.5, 35, and 70 mg/kg bw	B6C3F1 mice (sex, strain, and number of animals not stated) bone marrow cells	mammalian chromosomal aberration assay; single intraperitoneal injection	non-genotoxic	17
Oxyquinoline	NR	23-h exposure time: 0, 25, 50, and 100 mg/kg bw 42-h exposure time: 0, 17.5, 35, and 70 mg/kg bw	B6C3F1 mice (sex, strain, and number of animals not stated) bone marrow cells	sister chromatid exchange assay; single intraperitoneal injection	non-genotoxic	17
Oxyquinoline	NR	2-h exposure time: 500 mg/kg bw 12-h exposure time: 100, 150, and 250 mg/kg 24-h exposure time: 225 mg/kg bw	male Alpk:AP rats (number of animals not stated) hepatocytes	unscheduled DNA synthesis test; single oral dose by gavage	non-genotoxic	17
Oxyquinoline	NR	0, 7, 17.5, or 35 mg/kg bw	NMRI mice (male and female; number of animals not stated) peripheral blood cells	OECD TG 474; erythrocyte micronucleus assay; intraperitoneal injection; 44- and 68-h exposure	non-genotoxic	17
Oxyquinoline	NR	0, 25, 50, or 100 mg/kg bw	male CD-1 mice (number of animals not stated) bone marrow cells	erythrocyte micronucleus assay; intraperitoneal injection; bone marrow samples at 24, 48 and 72 h after administration	genotoxic	17

DMSO = dimethyl sulfoxide; NR = not reported; OECD = Organisation for Economic Co-operation and Development; TG = test guidelines

Table 6. Ocular irritation studies

Test Article	Vehicle	Concentration/Dose	Test Population	Protocol	Results	Reference
IN VITRO						
Oxyquinoline Sulfate	saline	20%	3 bovine corneas	OECD TG 437; bovine corneal opacity and permeability test; 4-h treatment; negative control: saline; positive control: imidazole solution	in vitro irritation score: 134 (as the score was > 55, the test item is considered a test chemical inducing serious eye damage); controls gave expected results	4
ANIMAL						
Oxyquinoline	no vehicle	100%; 0.1 g	3 female New Zealand white rabbits	OECD TG 405; test substance administered to 1 eye; untreated eye served as control; evaluations performed 1, 24, 48 and 72 h post-administration and from day 4-7 (one animal evaluated from day 4-20)	irritating – redness and chemosis observed in all test animals; corneal opacity observed in 1 animal; Category 1 irritant based on GHS criteria	5
Oxyquinoline	NR	10%; 0.1 ml	8 New Zealand white rabbits (sex not stated)	ocular irritation assay; 72-h observation period	non-irritating	17

GHS = global harmonized system; OECD = Organisation for Economic Co-operation and Development; TG = test guidelines

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Final Report on the Safety Assessment of Oxyquinoline and Oxyquinoline Sulfate

ABSTRACT

Oxyquinoline is a heterocyclic phenol which is used as a fungicide and bactericide in cosmetic formulations at concentrations at, or less than 1.0%. Oxyquinoline is metabolized and excreted in the urine as glucuronides. The acute oral LD_{50} toxicity in rats was 1.2 g/kg. In subchronic studies, no deaths occurred in male and female rats at 5 doses up to 12,000 ppm or in male and female mice up to doses of 6000 ppm. Solid 100% Oxyquinoline was mildly irritating to rabbit skin and a 100 mg dose of Oxyquinoline was only slightly irritating to the eye. No sensitization test data were available for either of these cosmetic ingredients. Oxyquinoline and Oxyquinoline Sulfate were mutagenic when assayed using the Ames procedure with metabolic activation. Mutagenic activity was also demonstrated in the mouse lymphoma assay. Oxyquinoline was noncarcinogenic in several oral rodent feeding studies. The data from this negative oral carcinogenic assay were judged to be insufficient to evaluate the safety of use of Oxyquinoline and Oxyquinoline Sulfate when cosmetic products containing these ingredients are applied to the skin.

It is concluded that the available carcinogenicity and sensitization test data are insufficient to support a conclusion on the safety of Oxyquinoline and Oxyquinoline Sulfate as used in cosmetic products.

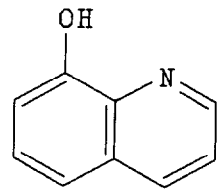
INTRODUCTION

THE FOLLOWING REPORT IS A LITERATURE review on the chemistry, uses, and toxicology of Oxyquinoline and Oxyquinoline Sulfate. In cosmetic formulations, these compounds are used as fungicides and oxidation stabilizers.

CHEMICAL AND PHYSICAL PROPERTIES

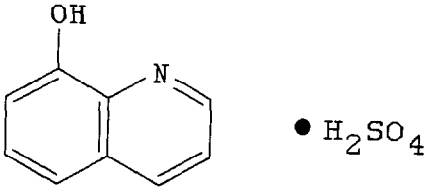
Definition and Chemical Structure

Oxyquinoline is a heterocyclic phenol amine that conforms to the formula (Estrin et al., 1982):



Other names for Oxyquinoline (CAS No. 148-24-3) include: 8-hydroxyquinoline, 8-quinolinol, oxine, hydroxybenzopyridine, oxybenzopyridine, phenopyridine, oxychinolin, bioquin, quinophenol, 8-oxychinolin, chinosol, fennosan HF-15, and phenoxypyridine (Estrin et al., 1982; Kabara, 1984; Kynoch and Lloyd, 1976; Rosoff, 1974; Sax, 1979; Windholz, 1983).

Oxyquinoline Sulfate (CAS No. 131-31-6) is the salt of Oxyquinoline and sulfuric acid that conforms to the structure (Estrin et al., 1982):



Properties

Oxyquinoline as a white powder or white crystals is virtually insoluble in water or ether. It is completely soluble in alcohol, acetone, chloroform, benzene, and aqueous mineral acids (Sax, 1979; Windholz, 1983).

The molecular weight of Oxyquinoline is 145.2. The melting point is 76°C, and the boiling point is 267°C (Sax, 1979; Windholz, 1983). The density of Oxyquinoline is 1.034. At 20°C, the pKa is 5.017, and the Ka is 1.21×10^{-6}. At 25°C, the pKa is 9.812 and the Ka is 1.54×10^{-10} (Weast, 1982). Infrared, Raman, and nuclear magnetic resonance spectra for Oxyquinoline have been published and analyzed in detail (Marchon et al., 1986; NTP, 1985). Oxyquinoline absorbs UV light at 243 and 318 nm (Grasselli, 1975).

Oxyquinoline Sulfate is a pale yellow, crystalline powder that has a saffron odor and a burning taste. It is freely soluble in water, soluble in 100 parts glycerol, and slightly soluble in alcohol. Oxyquinoline Sulfate is insoluble in ether (Windholz, 1983).

The molecular weight of Oxyquinoline Sulfate is 243. The melting point is 175–178°C (Windholz, 1983).

Method of Manufacture

Oxyquinoline can be prepared by the decarboxylation of 8-hydroxyquinoline-4-carboxylic acid. A second method of manufacture involves heating 2-aminophenol, 2-nitrophenol, and glycerine in sulfuric acid. Additionally, quinoline-8-sulfonic acid combines with caustic soda and water, or sulfonation of quinoline with oleum and fusion of the resulting sodium salt with sodium hydroxide at a temperature of 225°C will yield Oxyquinoline (International Agency for Research on Cancer (IARC), 1977).

Impurities

No information was available concerning any impurities in Oxyquinoline or Oxyquinoline Sulfate.

Cosmetic Use

Oxyquinoline is used as a fungicide and oxidation stabilizer in cosmetic and toilet preparations, including hair tonics and dressings, and miscellaneous skin and hair

products. Oxyquinoline is used in topical preparations only and has the potential to come in contact with all skin surfaces. The activity of Oxyquinoline against various microorganisms is summarized in Table 1.

Voluntary filing of product information data with the Food and Drug Administration (FDA) by cosmetic manufacturers and formulators must conform to the format of concentration ranges and product categories as described in Title 21 Part 720.4 of the Code of Federal Regulations (21 CFR 720.4). Since certain cosmetic ingredients are supplied to the formulator at less than 100% concentration, the concentration reported by the formulator may not necessarily reflect the actual concentration in the finished product; the actual concentration would be a fraction of that reported to the FDA. The fact that data are submitted within the framework of a "concentration range" provides the opportunity for overestimation of the actual concentration of an ingredient in a particular product. An entry at the lowest end of a concentration ranged is considered the same as one entered at the highest end of the range, thus introducing the possibility of a 2- to 10-fold error in the assumed concentration of the ingredient.

There are five reported uses of Oxyquinoline in cosmetic hair and skin preparations at concentrations at or below 1.0% (FDA, 1989).

International Use

Oxyquinoline and its sulfate are provisionally approved for use by the European Economic Community (EEC) with specifications for use at 0.3% as a stabilizer for hydrogen peroxide in rinse-off and non-rinse-off hair-care preparations. The concentration of oxyquinoline in preparations for "leave-on" skin hygiene products is limited to 0.02% (200 μg/ml), "leave-on" foot hygiene products to 0.04% and oral hygiene products to 0.01%. Labeling that indicates the presence of Oxyquinoline in these products are required (EEC, 1990). Oxyquinoline Sulfate is also approved for use in Japan (NIKKO Chemical, 1989).

NONCOSMETIC USE

Oxyquinoline and oxyquinoline sulfate are used as reagents for detection of bismuth, with which they form a red-orange or red-violet color upon interaction.

Table 1. Activity of Oxyquinoline Against Various Infective Agents

Test organisms (10^6 CFU/ml)	*Minimal inhibitory concentration (g/ml) Oxyquinoline used in serial dilution test*
Staphylococcus aureus	4
Escherichia coli	64
Klebsiella pneumoniae	64
Pseudomonas aeruginosa	128
Pseudomonas fluorescens	128
Pseudomonas cepacia	128
Candida albicans	128–256
Aspergillis niger	256–512
Penicillium notatum	128–256

Source: Kabara, 1984.

Oxyquinoline and its sulfate are also used as chelating agents in analysis of trace metals in industry (Greenberg and Lester, 1954; Kabara, 1984; Windholz, 1983).

Oxyquinoline and Oxyquinoline Sulfate are categorized as antifungal or antibacterial ingredients for over-the-counter drug use. Both are classified as Category IIISE; existing data are insufficient to permit classification at this time as either safe or unsafe, with reference to both safety and effectiveness of the product (OTC, 1988). [After the completion of this safety evaluation, FDA issued a proposed regulation that would ban the use of Oxyquinoline and Oxyquinoline Sulfate as active ingredients in topical antifungal drug products and skin protectant drug products due to the lack of submitted safety and effectiveness data (Federal Register, August 25, 1992).]

BIOLOGY

Intravenous administration of Oxyquinoline in rats resulted in the formation and excretion of glucuronide and sulfate conjugates. Glucuronides were found in the bile and the urine of albino Donryu rats at concentrations of 9 and 60% of the total dose, respectively. Sulfates formed in the rats were excreted in the urine, at concentrations up to 23% of the original dose (Kiwada et al., 1977; NTP, 1985).

Upon oral administration of Oxyquinoline to rats, increased amounts of iron were deposited in many tissues. This effect was proportional to the amount of iron available in the diet of the rats tested (Williams and Yamamoto, 1972; Yamamoto et al., 1971).

Oxyquinoline has also been implicated in the response of cells to certain chemicals (heat-shock or stress-related responses), and it has been suggested as one factor responsible for activation of certain latent viral infections in cells (Geelen et al., 1988).

TOXICOLOGY

Acute Oral Toxicity

In rats, the oral LD_{50} was 1.2 g/kg body weight (Association of American Pesticide Control Officials, Inc. (AAPCO), 1966).

In mice, the intraperitoneal LD_{50} of Oxyquinoline in 0.5% methylcellulose was 48 mg/kg (Bernstein et al., 1963).

The reported LD_{20} in guinea pigs was 1.2 g/kg body weight (Stecher, 1968).

When administered subcutaneously to rats, the LD_{50} for Oxyquinoline was 500 mg/animal. Acute percutaneous toxicity in rats, using Oxyquinoline dissolved in an appropriate solvent, was greater than 4 ml/kg body weight (maximum practical dose) (IARC, 1977).

Short-Term Toxicity

Fifteen day feeding studies were performed using male and female F344/N rats. Groups containing 5 male and 5 female rats were fed diets containing 0, 3,000, 6,000, 12,000, 25,000, or 50,000 ppm Oxyquinoline. Three male rats, two receiving 50,000 ppm, and one receiving 25,000 ppm died during the course of the study. None of the female rats died. Rats of both sexes in the highest dose groups experienced weight loss, when compared with untreated controls.

Fifteen-day feeding studies were performed using male and female $B6C3F_1$ mice. Groups consisting of 5 males and 5 females received the same doses as described above for rats. All mice receiving 25,000 and 50,000 ppm Oxyquinoline died prior to the completion of the study. Mice receiving 12,000 ppm Oxyquinoline lost weight (NTP, 1985).

Subchronic Toxicity

Nine male Fischer rats were fed a diet containing 0.8% Oxyquinoline for a period of 16 weeks, followed by a 10-week period on a control diet. Mean body weights were lower when compared with untreated controls. Both liver and spleen weights (g/100 g body weight) were increased in the rats fed the diets containing Oxyquinoline (Yamamoto et al., 1971).

Thirteen-week feeding studies were performed on F344/N male and female rats, five of each gender per group. The groups included those fed a diet containing 800, 1,500, 3,000, 6,000, or 12,000 ppm Oxyquinoline. There were no deaths in either gender during the study. Male rats fed the 12,000 ppm Oxyquinoline diet had mean body weights that were 18% lower when compared with untreated controls. Female rats fed 6,000 or 12,000 ppm Oxyquinoline had mean body weights that were 10.5% and 9.5% lower, respectively. All animals were necropsied at the end of the study. No compound related lesions were found in any of the animals of either gender (NTP, 1985).

Thirteen week feeding studies were conducted using male and female $B6C3F_1$ mice, five of each gender per group. The six groups included those fed a diet containing 400, 800, 1,500, 3,000, or 6,000 ppm Oxyquinoline. No compound-related deaths occurred. Male mice had mean body weights that were 11% lower than untreated controls in all groups. Female mice receiving the highest dose had mean body weights that were 10% lower than controls. The tissues from mice of the highest dose group collected at necropsy and specimens were examined microscopically, no compound-related lesions were detected (NTP, 1983).

Dermal Toxicity, Parenteral Studies

The irritant effects of Oxyquinoline were studied using an aqueous preparation painted on the skin of six rabbits (procedure in Code of Federal Regulations, Section 1500.41). After 72 h of treatment, all of the rabbits had slight to moderate erythema. The primary irritation index was 2.8, and the conclusion was that Oxyquinoline was a "moderate irritant to rabbit skin" (Kynoch and Liggett, 1976).

Six New Zealand rabbits received 0.5 g solid Oxyquinoline on occlusive patches to test the irritancy of oxyquinoline. The compound was applied to both intact and scarified skin. The duration of contract was 24 h. Results were scored at 24 and 72 h, 5 and 7 days after application. The index of irritation according to the Draize (1944) method was 0.66 at 24 and 72 h after application. After 5 and 7 days, the score was 0. Specimens of the treated skin were free of compound-related lesions, and Oxyquinoline was mildly irritating when applied to the skin of rabbits (Conan and Siou, 1979).

Ocular Irritation

The irritant effects of Oxyquinoline on the rabbit conjunctiva were studied using six animals. An Oxyquinoline dose of 100 mg was placed in the conjunctival sac, with the

untreated eye serving as a control. Four of the animals had opacity of the cornea and diffuse red conjunctivae. Overall, five of the six animals had ocular irritation. Oxyquinoline was considered an ocular irritant (Kynoch and Liggett, 1976).

Six New Zealand rabbits were used to study the irritant effects of Oxyquinoline to the conjunctivae. An Oxyquinoline dose of 100 mg was placed into the conjunctival sac of the left eye, and the right eye of each rabbit served as a control. The eyes were not rinsed after application. The eyes were scored one hour after application, then 1, 2, 3, 4, and 7 days after application of Oxyquinoline. The maximum index of irritation was 15.3 (maximum score 110), which occurred 1 day after application of Oxyquinoline. After day 4, there was no evidence of irritation. Oxyquinoline was slightly irritating when applied to the conjunctival sac of rabbits (Conan and Siou, 1979).

Acute Inhalation Toxicity

Five male and five female rats, CD strain, were used to test the effects of inhalation of Oxyquinoline. A droplet aerosol was produced by atomizing the formulation in a nebulizer. The 10 animals were exposed at the same time in a wine mesh compartment cage placed inside the 130 L exposure chamber which had an air flow of 25 L/min. Exposure was continuous for a 6-h period. LC_{50} values of both male and female rats were greater than 1.21 g/m^3. Animals were necropsied 14 days postexposure. No deaths occurred during the study, and no signs of either toxicity or irritancy were observed in the test animals (Coombs et al., 1979).

MUTAGENICITY

The mutagenic activity of Oxyquinoline was studied using the Ames bioassay (Hollstein et al., 1978). Four strains of *Salmonella typhimurium* were used: TA 98, TA 100, TA 1535, and TA 1537. Each strain was tested, both with and without metabolic activation, by liver S-9 fraction. Oxyquinoline was a mutagen in the presence of S-9 mixture, based on the results of those tests.

Nagao et al. (1977) tested the mutagenicity of Oxyquinoline and Oxyquinoline Sulfate at 200 and 500 μg/plate, respectively, in the Ames assay using *S. typhimurium* strains TA 98 and TA 100. It was determined that both compounds, when assayed in the presence of S-9 mixture, were mutagenic to both test strains.

Oxyquinoline was classified as a mutagen, upon metabolic activation with and without S-9 supernatant fraction, by Talcott et al. (1976). Ames testing was performed using TA 98, TA 100, TA 1535, and TA 1537 strains at an Oxyquinoline concentration of 100 μg/plate. Oxyquinoline was mutagenic in strain TA 100 with metabolic activation, but not in the other test strains.

Gocke et al. (1981) tested cosmetic ingredients licensed by the European Communities for mutagenicity. Using the strains TA 98, TA 100, TA 1535, and TA 1537 in the Ames test, Oxyquinoline at a test concentration of 600 μg/plate was positive only in strain TA 100 in the presence of metabolic activation.

Sideropolous and Specht (1984), tested Oxyquinoline and Oxyquinoline Sulfate for mutagenic activity with and without the presence of liver S-9 fraction in four *S. typhimurium* strains TA98, TA 100, TA 1535, and TA 1537. The mutagenic assay was performed at the minimum inhibitory concentration of 125 μg/ml for Oxyquinoline and 500 μg/ml for Oxyquinoline Sulfate. Mutagenicity tests were positive only in the two

strains, TA 98 and TA 100 in which the S-9 liver fraction was included. Additionally, induction of mutations to streptomycin resistance was tested. Oxyquinoline was not mutagenic in this test system, even in the presence of liver S-9 fraction (Sideropolous and Specht, 1984). Oxyquinoline was tested at concentrations of 10 μM and 100 μM in Ehrlich ascites cells and *Escherichia coli* cells. In these assay systems, Oxyquinoline was mutagenic.

Oxyquinoline was positive in the Ames test performed by Epler et al. (1977). In the presence of hepatic enzymes, induced by Aroclur and phenobarbital, Oxyquinoline had mutagenic activity in two strains. The induction of chromatid aberrations was also tested. Oxyquinoline did induce breaks in chromatids, as well as achromic lesions.

Using the L5178Y tk^+/tk^- mouse lymphoma cell forward mutation assay, McGregor et al. (1988) tested 18 chemicals, including Oxyquinoline, for mutagenesis. In this test system, Oxyquinoline was mutagenic.

Oxyquinoline binds to DNA in the presence of liver extract (Kubinski et al., 1981).

Results from the mutagenesis tests are summarized in Table 2.

CARCINOGENICITY

Oxyquinoline was tested for carcinogenic potential by Boyland et al. (1966). Twenty BALB/c female mice were given twice weekly intravaginal doses of 1% Oxyquinoline suspended in gum tragacanth. The total number of treatments was 100. One mouse developed a squamous papilloma of the cervix. Oxyquinoline was not a carcinogen in this assay system.

Two groups of 15 male Fischer rats were fed diets containing 0.8% Oxyquinoline for 52 or 78 weeks. There were five deaths in the rats of the 52-week group, and 2 deaths occurred in the rats of the 78-week study. The authors did not report whether or not the deaths were compound related. Both groups had mean body weights that were less than untreated controls, and hepatic and splenic weights (g/100 g body weight) were increased. No compound-related lesions were observed at necropsy (Yamamoto et al., 1971).

TABLE 2. MUTAGENICITY OF OXYQUINOLINE

	Salmonella typhimurium								
	TA 98		*TA 100*		*TA 1535*		*TA 1537*		
Dose/plate	*(−)S-9*	*(+)S-9*	*(−)S-9*	*(+)S-9*	*(−)S-9*	*(+)S-9*	*(−)S-9*	*(+)S-9*	*Reference*
Oxyquinoline	(−)	(+)	(−)	(+)	—	—	—	—	Nagao et al., 1978
Oxyquinoline Sulfate	(−)	(+)	(−)	(+)	—	—	—	—	Nagao et al., 1978
Oxyquinoline	(−)	(+)	(−)	(+)	(−)	(−)	(−)	(−)	Sideropolous and Specht, 1984
Oxyquinoline Sulfate	(−)	(+)	(−)	(+)	(−)	(−)	(−)	(−)	Sideropolous and Specht, 1984
Oxyquinoline	(−)	(−)	(−)	(+)	(−)	(−)	(−)	(−)	Gocke et al., 1981
Oxyquinoline	(−)	(−)	(−)	(+)	(−)	(−)	(−)	(−)	Talcott et al., 1976
L5178Y mouse lymphoma				positive					McGregor et al., 1988
DNA cell-binding assay				positive					Kubinski et al., 1981

Two-year feeding studies with diets containing 1500 or 3000 ppm (0.15 or 0.3%) Oxyquinoline were performed using 50 male and 50 female F344/N rats. Mortality of animals consuming the test diet was not significantly greater than controls. Mean body weights for treated animals were lower than body weights of the untreated control animals. No significant lesions were observed in the test animals at necropsy (NTP, 1985).

Fifty male and 50 female B6C3F$_1$ strain mice were fed diets containing either 1500 or 3000 ppm (0.15 or 0.3%) Oxyquinoline for two years. Survival for both sexes was comparable to survival of untreated control animals. The mean body weights, for both sexes at both doses, were lower then body weights of control animals. No compound-related lesions were noted in any animals at necropsy (NTP, 1985).

Male and female F344 rats, thirty per group, were fed diets containing 0.1% oxyquinoline for 104 weeks. A control group of 31 males and 44 females was included in the test program. Three male rats in the treated group, but none in the control group, developed hyperplastic nodules in the liver. Seven rats in the test group and 8 in the control developed testicular tumors, and one rat in the treated group, and none in the control had neoplasms of the spleen. These results were not statistically significant. There were no significant differences in the incidences of neoplasms reported for either the treated test group or the control group. Under the procedures used, Oxyquinoline was judged to be noncarcinogenic to the male or female rat (Fukushima et al., 1981).

Clayson and Cooper (1970) also reported no carcinogenicity when Oxyquinoline was implanted in the urinary bladders of mice (strain and number unspecified) in either cholesterol or paraffin wax. Concentrations of Oxyquinoline were 12.5 and 20%, respectively. In both vehicles, Oxyquinoline was negative for carcinogenic activity.

Boyland et al. (1987), in an article concerning acceptable levels of tumor promoters, listed Oxyquinoline as a tumor promoter in the category of chelating agents. The International Agency for Research on Cancer (1987) concluded that the evidence is inadequate to determine the carcinogenicity of Oxyquinoline in animals.

CLINICAL ASSESSMENT OF SAFETY

No data are currently available to assess the safety of Oxyquinoline in humans.

SUMMARY

Oxyquinoline is a heterocyclic phenol which is used as a fungicide and bactericide in cosmetic formulations at concentrations at, or less than 1.0%.

Oxyquinoline is metabolized and excreted in the urine as glucuronides. The acute oral LD_{50} toxicity in rats was 1.2 g/kg. The interperitoneal LD_{50} in mice was 0.48 g/kg. In subchronic studies no deaths occurred in groups of 5 male and 5 female rats at 5 doses up to 12,000 ppm or in 5 male and 5 female mice up to doses of 6000 ppm. Loss of weight, as compared with groups of 5 nontreated male and female control groups, occurred at doses of 12,000 ppm for male and 6,000 and 12,000 ppm for female. Male mice lost weight at the lowest test dose of 400 ppm, and females, at the highest dose of 6,000 ppm. Solid 100% oxyquinoline was mildly irritating to rabbit skin. A 100 mg dose of Oxyquinoline was only slightly irritating to the eye.

Oxyquinoline and Oxyquinoline Sulfate were mutagenic in 2 of 4 *S. typhimurium* strains when assayed using the Ames procedure with metabolic activation. Mutagenic activity was also demonstrated in the mouse lymphoma assay.

Oxyquinoline was noncarcinogenic in several rodent feeding studies. The International Agency for Research on Cancer concluded that the existing evidence is inadequate to determine carcinogenicity in animals.

DISCUSSION

The Expert Panel notes that oxyquinoline is an active cosmetic ingredient that binds to DNA and is mutagenic in some assay systems. The CIR Expert Panel concurs with the position of the Environmental Protection Agency that bacterial mutagenic assay systems are not appropriate for assessing the mutagenic potential of microbiocides in mammalian systems. However, the Expert Panel did not consider that the available negative oral carcinogenic assays were sufficient to evaluate the safety of use of Oxyquinoline in humans who are exposed to this ingredient in cosmetic products applied to the skin. Therefore, a skin carcinogenicity study in one animal species is needed. Human skin irritation and sensitization (including photosensitization) data are also needed before a conclusion on the safety of use of Oxyquinoline and Oxyquinoline Sulfate in cosmetic products can be made.

Section 1, paragraph (p) of the CIR Procedures states that "A lack of information about an ingredient shall not be sufficient to justify a determination of safety." In accordance with Section 30(j)(2)(A) of the CIR Procedures, the Panel informed the public of its decision that the data on Oxyquinoline and Oxyquinoline Sulfate are insufficient to determine whether these ingredients, under each relevant condition of use, are either safe or unsafe. The Panel released a Notice of Insufficient Data Announcement on November 12, 1990 outlining the data needed to assess the safety of Oxyquinoline and Oxyquinoline Sulfate. The types of data required included: (a) dermal carcinogenesis (mouse) if (a) is negative, (b) skin irritation (human), (c) skin sensitization and photosensitization (human).

No offer to supply results from a dermal carcinogenicity study was received. In accordance with Section 45 of the CIR Procedures, the Expert Panel will issue a Final Safety Evaluation Report—Insufficient Data. When the requested new data become available, the Panel will reconsider the Final Report in accordance wtih Section 46 of the CIR Procedures, Amendment of a Final Report.

CONCLUSION

The CIR Expert Panel concludes that the available data are insufficient to support the safety of Oxyquinoline and Oxyquinoline Sulfate as used in cosmetic products.

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Final Amended Report on the Safety Assessment of Oxyquinoline and Oxyquinoline Sulfate as Used in Cosmetics[1]

Oxyquinoline is a heterocyclic phenol and Oxyquinoline Sulfate is its salt, both of which are described as cosmetic biocides for use in cosmetic formulations. In an earlier Cosmetic Ingredient Review (CIR) safety assessment, the available data were found insufficient to support safety. Currently, some uses are reported to the Food and Drug Administration (FDA) by industry, but industry reports to CIR indicate no use. In Europe, Oxyquinoline and Oxyquinoline Sulfate are accepted for use as stabilizers for hydrogen peroxide in rinse-off and leave-on hair care preparations, with concentration limitations. Oxyquinoline is metabolized and excreted in the urine as glucuronides. Oxyquinoline and Oxyquinoline Sulfate exhibit little acute or subchronic toxicity in animal studies. A 100-mg dose of Oxyquinoline was only slightly irritating to the eye. Oxyquinoline and Oxyquinoline Sulfate were genotoxic in certain *Salmonella typhimirium* strains with metabolic activation and in a mouse lymphoma assay. There was some evidence of increased chromosome aberrations in an in vitro study, and an increase in sister-chromatid exchanges (but not chromosome aberrations) in rats treated with Oxyquinoline, but no genotoxicity was found in a *Drosophilia* sex-linked recessive lethal test, mouse bone marrow micronucleus test, a rat bone marrow and hepatocyte micronucleus test, and unscheduled DNA synthesis in rat hepatocytes. Oxyquinoline did bind to DNA in the presence of liver enzymes. Although the International Agency for Research on Cancer concluded that the existing evidence is inadequate to determine carcinogenicity in animals, Oxyquinoline was noncarcinogenic in several rodent feeding studies, and newly available studies using genetically altered mice, in one case carrying the human c-Ha-ras gene, demonstrated that Oxyquinoline was not carcinogenic. In clinical tests, Oxyquinoline is neither an irritant nor a sensitizer when tested at 1% in petrolatum. The available data demonstrate that Oxyquinoline and Oxyquinoline Sulfate are safe as stabilizers for hydrogen peroxide in rinse-off hair care cosmetic products in the present practices of use. For leave-on cosmetic products, however, the absence of impurities and ultraviolet (UV) absorption data resulted in a finding that the available data are insufficient to support safety. The data needed in order to complete the safety assessment of Oxyquinoline and Oxyquinoline Sulfate in leave-on cosmetic products are (1) UV absorption data—if significant absorption occurs, then photoirritation/photosensitization data will be needed; and (2) data on impurities.

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[1]Reviewed by the Cosmetic Ingredient Review (CIR) Expert Panel.

INTRODUCTION

This amended safety assessment updates and supercedes an earlier Cosmetic Ingredient Review (CIR) safety assessment of Oxyquinoline and Oxyquinoline Sulfate (Elder 1992). Oxyquinoline and Oxyquinoline Sulfate are currently described as cosmetic biocides, although in Europe their approval (with concentration limitations) is for use as stabilizers for hydrogen peroxide in rinse-off and leave-on hair care preparations.

CHEMISTRY

Definition and Chemical Structure

Oxyquinoline

Oxyquinoline is a heterocyclic phenol amine that conforms to the formula shown in Figure 1 (Pepe et al. 2002). As given in Estrin et al. (1982a), Sax (1979), Windholz (1983), Kynoch and Lloyd (1976a), and Kabara (1984), other names for Oxyquinoline (CAS no. 148-24-3) include:

- 8-hydroxyquinoline,
- 8-quinolinol,
- oxine,
- hydroxybenzopyridine,
- oxybenzopyridine,
- phenopyridine,
- oxychinolin,
- bioquin,
- quinophenol,
- 8-oxychinolin,
- chinosol,
- fennosan HF-15, and
- phenoxypyridine.

Oxyquinoline Sulfate

Oxyquinoline Sulfate (CAS no. 131-31-6) is the salt of Oxyquinoline and sulfuric acid that conforms to the structure shown in Figure 2 (Estrin et al. 1982a).

Chemical and Physical Properties

Oxyquinoline

Oxyquinoline is a white powder or crystals, and is virtually insoluble in water or ether. It is completely soluble in alcohol,

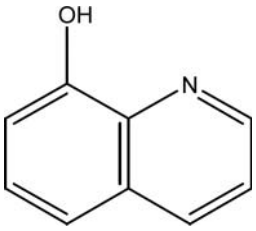

FIGURE 1
Formula for Oxyquinoline.

acetone, chloroform, benzene, and aqueous mineral acids (Windholz 1983; Sax 1979).

The molecular weight for Oxyquinoline is 145.2. The melting point is 76°C, and the boiling point is 267°C (Windholz 1983; Sax 1979). The density of Oxyquinoline is 1.034. At 20°C, the pK_a is 5.017, and the K_a is 1.21×10^{-6}. At 25°C, the pK_a, is 9.812 and the K_a is 1.54×10^{-10} (Weast et al. 1982). Infrared spectra, Raman spectra, and nuclear magnetic resonance spectra for Oxyquinoline have been published and analyzed in detail (Marchon 1986; NTP 1985). Oxyquinoline absorbs ultraviolet (UV) light at 243 and 318 nm (Grasselli 1975).

Oxyquinoline Sulfate

Oxyquinoline Sulfate is a pale yellow, crystalline powder that has a saffron odor and a burning taste. It is freely soluble in water, soluble in 100 parts glycerol, and slightly soluble in alcohol. Oxyquinoline Sulfate is insoluble in ether. The molecular weight of Oxyquinoline Sulfate is 243. The melting point is 175°C to 178°C (Windholz 1983).

Method of Manufacture

Oxyquinoline

Oxyquinoline can be prepared by the decarboxylation of 8-hydroxyquinoline-4-carboxylic acid. A second method of manufacture involves heating 2-aminophenol, 2-nitrophenol, and glycerine in sulfuric acid. Additionally, quinoline-8-sulfonic acid combines with caustic soda and water, or sulfonation of quinoline with oleum and fusion of the resulting sodium salt with sodium hydroxide at a temperature of 225°C will yield Oxyquinoline [International Agency for Research on Cancer (IARC) 1977].

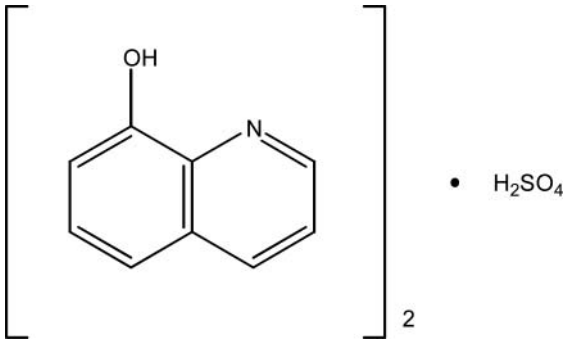

FIGURE 2
Formula for Oxyquinoline Sulfate.

Oxyquinoline Sulfate

No information was available on the method of manufacture of Oxyquinoline Sulfate.

Impurities

No information was available concerning any impurities in Oxyquinoline or Oxyquinoline Sulfate.

USE

Cosmetic

As given in the *International Cosmetic Ingredient Dictionary and Handbook*, Oxyquinoline and Oxyquinoline Sulfate currently are described as cosmetic biocides (Pepe et al. 2002). Additional uses had previously been described, including: fungicides, bacteriocides, and oxidation stabilizers in cosmetics (Elder 1992). Wilkinson and Moore (1982) in *Harry's Cosmetology* included Oxyquinoline (8-hydroxyquinoline) and the potassium salt of Oxyquinoline Sulfate as preservatives used in cosmetics and toilet preparations.

According to the European Commision (EC), Oxyquinoline and its sulfate are included in the list of substances that cosmetic products must not contain unless used at 0.3% (calculated as base) as a stabilizer for hydrogen peroxide in rinse-off hair-care preparations or at 0.03% for the same purpose in non rinse-off hair care preparations (EC 1999).

According to the Ministry of Health, Labor, and Welfare of Japan (MHLW), neither Oxyquinoline or Oxyquinoline Sulfate are included on a negative list (MHLW 2000a) or on a list of ingredients for which there are restrictions to use in cosmetics (MHLW 2000b). Preservatives used in cosmetics in Japan must be those in a table listing acceptable preservatives and their use concentrations, but neither Oxyquinoline or Oxyquinoline Sulfate are included on that list (MHLW 2000c).

Industry reports to the Food and Drug Administration (FDA) in 2002 include the uses of these ingredients shown in Table 1. Information provided to the Cosmetic, Toiletry, and Fragrance Association (CTFA) indicates that these ingredients were used in several types of cosmetics at the concentrations shown in Table 1 (CTFA 2002). Historical uses and concentrations (FDA 1984) are given in the last column in Table 1.

Noncosmetic

Oxyquinoline and Oxyquinoline Sulfate are used as reagents for detection of bismuth—the reaction forms a red-orange or red-violet color. Oxyquinoline and its sulfate are also used as chelating agents in analysis of trace metals in industry (Windholz 1983; Kabara 1984; Greenberg 1954).

TABLE 1
Use of Oxyquinoline and Oxyquinoline Sulfate in cosmetic products

Product type (total number of products) (FDA 2002)	Number of products with ingredient (FDA 2002)	Concentration of use (CTFA 2002)	Historical concentration of use (FDA 1984)
Oxyquinoline			
Fragrance preparations			
Powders (273)	—	0.1%	—
Noncoloring hair preparations			
Rinses (42)	—	0.1%	—
Hair tonics, dressings, etc. (577)	1	—	<1%
Other (276)	1	—	0.1–1%
Skin care preparations			
Other (715)	2	—	0.1–1%
2001 total uses/ranges for Oxyquinoline	**4**	**0.1%**	**0.1–1%**
Oxyquinoline Sulfate			
Fragrance preparations			
Powders (273)	—	0.05%	—
Noncoloring hair preparations			
Hair straighteners (63)	—	0.01%	—
Permanent waves (211)	2	0.01%	<0.1%
Rinses (42)	—	0.1%	—
Hair tonics, dressings, etc. (577)	1	—	—
Hair-coloring preparations			
Dyes and colors (1588)	1	0.05%	—
Bleaches (120)	—	0.05%	—
Other (59)	1	—	<0.1%
Skin care preparations			
Body and hand lotions, creams, etc. (827)	2	—	<0.1%
Suntan preparations			
Suntan gels, creams, and liquids (131)	—	—	<0.1%
2001 total uses/ranges for Oxyquinoline Sulfate	**7**	**0.01–0.1%**	**<0.1%**

Liu et al. (1994) reported that copper-8-oxyquinolinolate is used to treat fresh sawn softwood lumber to prevent the development of sapstain, a discoloration in wood caused by microbial growth.

Oxyquinoline Sulfate is currently listed in the Code of Federal Regulations among those drugs whose safety and effectiveness has not been demonstrated in both the skin protectant [21CFR310.545(a)(18)(ii)] and the topical antifungal categories [21CFR545.310(a)(22)(ii)].

GENERAL BIOLOGY

Biocidal Activity

The activity of biocides against various microorganisms can be determined in a serial dilution test (NCCLS 1999). In this test, the biocide is diluted to find the lowest concentration at which it is effective in killing the particular organism. The minimum inhibitory concentrations for Oxyquinoline are given in Table 2 (Kabara 1984).

TABLE 2
Minimum inhibitory concentrations of Oxyquinoline for various test organisms in a serial dilution test (Kabara 1984)

Test organism (10^6 CFU/ml)	Minimum inhibitory concentration (μg/ml)
Staphylococcus aureus	4
Escherichia coli	64
Klebsiella pneumoniae	64
Pseudomonas aeruginosa	128
Pseudomonas fluorescens	128
Pseudomonas cepacia	128
Candida albicans	128–256
Aspergillis niger	256–512
Penicillium notatum	128–256

Note. CFU, colony forming units.

Liu et al. (1994) reported that copper-8-oxyquinolinolate is toxic to *Bacillus cereus* in culture, but that neither copper nor 8-hydroxyquinoline (maximum concentration tested of 2 ppm) were found to be toxic.

Absorption, Distribution, Metabolism, and Excretion

Intravenous administration of Oxyquinoline in rats resulted in the formation and excretion of glucuronide and sulfate conjugates. Glucuronides were found in the bile and the urine of albino Donryu rats at concentrations of 9% and 60% of the total dose, respectively. Sulfates formed in the rats were excreted in the urine, at concentrations up to 23% of the original dose (NTP 1985; Kiwada et al. 1977).

Upon oral administration of Oxyquinoline to rats, increased amounts of iron were deposited in many tissues. This effect was proportional to the amount of iron available in the diet of the rats tested (Yamamoto 1971; Williams and Yamamoto 1972).

Oxyquinoline has also been implicated in the response of cells to certain chemicals (heat-shock or stress-related responses), and it has been suggested that it could be one of the factors responsible for activation of certain latent viral infections in cells (Geelen et al. 1988).

ANIMAL TOXICOLOGY

Acute Toxicity

According to the Association of American Pesticide Control Officials, Inc. (AAPCO), the oral LD_{50} was 1.2 g/kg body weight in rats (AAPCO 1966).

In mice, the intraperitoneal LD_{50} of mice (of Oxyquinoline in 0.5% methylcellulose) was 48 mg/kg (Bernstein et al. 1963).

When administered subcutaneously to rats, the LD_{50} for Oxyquinoline was 500 mg/animal (IARC 1977).

Acute percutaneous toxicity in rats, using Oxyquinoline dissolved in an appropriate solvent, was greater than 4 ml/kg body weight, which was considered the maximum practical dose (Kynoch and Lloyd 1976b).

Short-Term Oral Toxicity

Oxyquinoline

The National Toxicology Program (NTP) conducted 15-day feeding studies using male and female F344/N rats (NTP 1985). Groups containing five male and five female rats were fed diets containing 0, 3000, 6000, 12,000, 25,000, or 50,000 ppm Oxyquinoline. Three male rats, two receiving 50,000 ppm and one receiving 25,000 ppm, died during the course of the study. None of the female rats died. Rats of both sexes in the highest dose groups experienced weight loss when compared to untreated controls.

Fifteen-day feeding studies also were performed using male and female $B6C3F_1$ mice. Groups consisting of five males and five females received the same doses as described above for rats. All mice receiving 25,000 and 50,000 ppm Oxyquinoline died prior to the completion of the study. Mice receiving 12,000 ppm Oxyquinoline lost weight and were emaciated (NTP 1985).

Subchronic Oral Toxicity

Oxyquinoline

Yamamoto et al. (1971) fed nine male Fischer rats a diet containing 0.8% Oxyquinoline for a period of 16 weeks, followed by a 10-week period on a control diet. Mean body weights were lower when compared to untreated controls. Both liver and spleen weights (g/100 g body weight) were increased in the rats fed the diets containing Oxyquinoline.

NTP (1985) performed 13-week feeding studies on F344/N male and female rats, five of each sex per group. The groups included those fed a diet containing 800, 1500, 3000, 6000, or 12,000 ppm Oxyquinoline. There were no deaths in either sex during the study. Male rats fed the 12,000 ppm Oxyquinoline diet had mean body weights that were 18% lower when compared to untreated controls. Female rats fed 6000 or 12,000 ppm Oxyquinoline had mean body weights that were 10.5% and 9.5% lower, respectively. All animals were necropsied at the end of the study. No compound-related lesions were found in any of the animals of either sex.

Thirteen-week feeding studies also were conducted using male and female $B6C3F_1$ mice, five of each sex per group. The six groups included those fed a diet containing 400, 800, 1500, 3000, or 6000 ppm Oxyquinoline. No compound-related deaths occurred. Male mice had mean body weights that were 11% lower than untreated controls in all groups. Female mice receiving the highest dose had mean body weights that were 10% lower than controls. The tissues from mice of the highest-dose group collected at necropsy and specimens were examined microscopically, no compound-related lesions were detected (NTP 1985).

Dermal Toxicity

Oxyquinoline

Kynoch and Liggett (1976b) studied the irritant effects of Oxyquinoline using an aqueous preparation painted on the skin of six rabbits (procedure in Code of Federal Regulations, Section 1500.41). Given the insolubility of Oxyquinoline in water noted earlier, the nature of the "aqueous preparation" was unclear. After 72 h of treatment, all of the rabbits had slight to moderate erythema. The primary irritation index was 2.8, and the authors concluded that Oxyquinoline was a moderate irritant in this test system.

Conan and Siou (1979) reported that six New Zealand rabbits received 0.5 g solid Oxyquinoline on occlusive patches to test the irritancy of Oxyquinoline. The compound was applied to both intact and scarified skin. The duration of contact was 24 h. Results were scored at 24 h, 72 h, 5 days, and 7 days after application. The index of irritation according to the Draize method was 0.66 at 24 and 72 h after application. After 5 and 7 days, the score was 0. Specimens of the treated skin were free of compound-related lesions, and the authors concluded that solid

Oxyquinoline was only mildly irritating when applied to the skin of rabbits.

Ocular Irritation

Oxyquinoline

Kynoch and Liggett (1976a) studied the irritant effects of Oxyquinoline on the rabbit eye using six animals. Oxyquinoline dose of 100 mg was placed in the conjunctival sac, with the untreated eye serving as a control. Four of the animals had opacity of the cornea and diffuse red conjunctivae. Overall, five of the six animals had ocular irritation. The authors considered Oxyquinoline to be an ocular irritant.

Conan and Siou (1979) used 6 New Zealand rabbits to study the irritant effects of Oxyquinoline to the eye. Oxyquinoline dose of 100 mg was placed into the conjunctival sac of the left eye, and the right eye of each rabbit served as a control. The eyes were not rinsed after application. The eyes were scored one hour after application, then 1, 2, 3, 4, and 7 days after application of Oxyquinoline. The maximum index of irritation was 15.3 (maximum score 110), which occurred 1 day after application of Oxyquinoline. After day 4, there was no evidence of irritation. The authors concluded that Oxyquinoline was slightly irritating when applied to the conjunctival sac of rabbits.

Acute Inhalation Toxicity

Oxyquinoline

Five male and five female rats, CD strain, were used to test the effects of inhalation of Oxyquinoline. A droplet aerosol was produced by atomizing the material in a nebulizer. The 10 animals were exposed at the same time in a wire mesh compartment cage placed inside the 130-L exposure chamber which had an air flow of 25 L/min. Exposure was continuous for a 6 h period. LC_{50} values of both male and female rats were greater than 1.21 g/m^3. Animals were necropsied 14 days post exposure. No deaths occurred during the study, and no signs of either toxicity or irritancy was observed in the test animals (Coombs 1979).

GENOTOXICITY

Bacterial Test Systems

Oxyquinoline

Talcott et al. (1976) classified Oxyquinoline as a mutagen, upon metabolic activation with S-9 supernatant fraction based on Ames testing using TA 98, TA 100, TA 1535, and TA 1537 strains at a Oxyquinoline concentration of 100 μg/plate. Oxyquinoline was mutagenic in strain TA 100 with metabolic activation, but not in the other test strains.

Oxyquinoline was positive in the Ames test performed by Epler et al. (1977). In the presence of hepatic enzymes, Aroclar, and phenobarbital, Oxyquinoline had mutagenic activity in two strains.

Hollstein et al. (1978) studied the mutagenic activity of Oxyquinoline using the Ames bioassay. Four strains of *S. typhimirium* were used: TA 98, TA 100, TA 1535, and TA 1537. Each strain was tested, both with and without metabolic activation by liver S-9 fraction. Oxyquinoline was a mutagen only in the presence of S-9 mixture.

Gocke et al. (1981) tested cosmetic ingredients licensed in Europe for mutagenicity, with and without metabolic activation. Using the strains TA 98, TA 100, TA 1535, and TA 1537 in the Ames test, Oxyquinoline at a test concentration of 600 ug/plate, was positive for mutagenic activity only in strain TA 100 in the presence of metabolic activation.

Oxyquinoline and Oxyquinoline Sulfate

Nagao et al. (1977) tested the mutagenicity of Oxyquinoline and Oxyquinoline Sulfate at 200 and 500 μg/plate, respectively, in the Ames assay using *S. typhimirium* strains TA 98 and TA 100. It was determined that both compounds, when assayed in the presence of S-9 mixture, were mutagenic to both test strains.

Sideropolous (1984) tested Oxyquinoline and Oxyquinoline Sulfate for mutagenic activity with and without the presence of liver S-9 fraction in four *S. typhimirium* strains TA98, TA 100, TA 1535, and TA 1537. The mutagenic assay was performed at the minimum inhibitory concentration of 125 μg/ml for Oxyquinoline and 500 μg/ml for Oxyquinoline Sulfate.

Mutagenicity tests were positive only in the two strains, TA 98 and TA 100 in which the S-9 liver fraction was included. Additionally, induction of mutations to streptomycin resistance were tested. Oxyquinoline was not mutagenic in this test system, even in the presence of liver S-9 fraction (Sideropolous 1984).

Mammalian Test Systems

Oxyquinoline

McGregor et al. (1988) tested 18 chemicals, including Oxyquinoline, for mutagenesis using the L5178Y tk$^+$/tk$^-$ mouse lymphoma cell forward mutation assay. In this test system, Oxyquinoline was mutagenic.

Ashby et al. (1989) used Oxyquinoline and Quinoline to compare and contrast unscheduled DNA synthesis and mitogenesis in the rat liver with carcinogenicity and genotoxicity findings. Male rats were given Oxyquinoline at levels up to 225 mg/kg for up to 24 h prior to sacrifice. Liver hepatocytes were isolated and unscheduled DNA synthesis and mitogenesis were determined. Quinoline was used as a positive control—it induced both unscheduled DNA synthesis and mitogenesis. Oxyquinoline was inactive for both end points. The authors suggested that assays for mitogenicity in the rat liver were better correlated with carcinogenicity than were genotoxicity assays.

Allavena et al. (1992), as part of a program to evaluate the carcinogenesis predictive value of genotoxicity tests, tested chemicals that were genotoxic in vitro, but not carcinogenic in vivo, using a battery of short-term in vivo genotoxicity assays. Oxyquinoline was negative in a micronucleus test using bone marrow and liver cells whereas the positive control, *N*-nitrosodimethylamine (NDMA), was clearly positive.

Oxyquinoline was only slightly active in inducing unscheduled DNA synthesis (only small increases and a small number of cells), whereas NDMA produced hefty increases in all cells. Oxyquinoline did not cause DNA fragmentation in hepatocyte DNA. The authors argued that in vivo genotoxicity test systems were preferable to in vitro genotoxicity tests.

Armstrong et al. (1992), in a study of appropriate cytotoxicity doses in Chinese hamster ovary cells in assays for chromosomal aberrations, reported that Oxyquinoline at 40 μM caused increases in chromosomal aberrations with little acute toxicity at 3 h incubation but considerable toxicity at 24 h. Higher concentrations of Oxyquinoline (50 to 70 μM) were also effective in producing aberrations. The authors concluded that a 24-h harvest effectively demonstrated the clastogenic effect of Oxyquinoline.

Shelby et al. (1993) examined the impact of a protocol modification of the micronucleus test in $B6C3F_1$ mice in which three daily doses were given, followed 24 h later by a single bone marrow/blood sample. In this protocol, intraperitoneal injection of 0.4 ml test material was done on three consecutive days. Animals were monitored twice daily. At 48 h after the last treatment, the mice were euthanized by CO_2 asphyxiation and bone marrow and peripheral blood smears were prepared. Doses of Oxyquinoline up to 43 mg/kg were negative. Shelby and Witt (1995) compared the results of in vivo mouse bone marrow micronucleus and chromosomal aberration tests, confirming the results above that Oxyquinoline is not genotoxic.

Miyagawa et al. (1995) conducted a study to examine the utility of the in vivo–in vitro hepatocyte replicative DNA synthesis (RDS) test as an early prediction assay for nongenotoxic mouse hepatocarcinogens. Oxyquinoline at 125 mg/kg (half the maximum tolerated dose) and 250 mg/kg failed to induce RDS. The authors suggested that RDS test results should be incorporated into cancer risk assessment.

Asakura et al. (1997) compared the ability of Oxyquinoline and Quinoline to produce chromosome aberrations, sister-chromatid exchanges (SCEs), or replicative DNA synthesis (RDS) in the liver of treated F344 rats. Quinoline at a single dose of 200 mg/kg and 28 repeated doses of 25 to 200 mg/kg induced chromosome aberrations, SCEs, and RDS. In addition, chromosome damage and SCEs were greater with the repeated doses, suggesting some cumulative effect. Oxyquinoline at 500 mg/kg (single or 28 repeated) failed to induce chromosome aberrations or RDS. SCEs were increased after a single dose, but values for the repeated dosings were actually lower, suggesting the absence of a cumulative effect. The authors stated that Oxyquinoline was essentially nongenotoxic to the rat liver.

Drosophila Test Systems

Oxyquinoline

Foureman et al. (1994) reported results of Oxyquinoline in the sex-linked recessive lethality test in male fruit flies. Administration of 1200 ppm Oxyquinoline by feeding or 2900 ppm by injection failed to cause any increase in sex-linked recessive lethal mutations compared to controls.

DNA Binding

Oxyquinoline

Kubinski et al. (1981) demonstrated that Oxyquinoline binds to DNA in the presence of liver extract.

CARCINOGENICITY

Oxyquinoline

Oxyquinoline was tested for carcinogenic potential by Boyland (1966). Twenty BALB/c female mice were given twice weekly intravaginal doses of 1% Oxyquinoline suspended in gum traganth. The total number of treatments was 100. One mouse developed a squamous papilloma of the cervix. Oxyquinoline was not a carcinogen in this assay system.

Clayson (1970) reported no carcinogenicity when Oxyquinoline was implanted in the urinary bladders of mice (strain and number unspecified) in either cholesterol or paraffin wax. Concentrations of Oxyquinoline were 12.5% and 20%, respectively. In both vehicles, Oxyquinoline was negative for carcinogenic activity.

Yamamoto et al. (1971) fed two groups of 15 male Fischer rats diets containing 0.8% Oxyquinoline for 52 or 78 weeks. There were five deaths in the rats of the 52-week group, and 2 deaths occurred in the rats of the 78-week study. The authors did not report whether or not the deaths were compound related. Both groups had mean body weights that were less than untreated controls, and hepatic and splenic weights (g/100 g body weight) were increased. There were no compound-related lesions observed at necropsy.

Fukushima (1981) fed male and female F344 rats, 30 per group, diets containing 0.1% Oxyquinoline for 104 weeks. A control group of 31 males and 44 females were included in the test program. Three male rats in the treated group, but none in the control group, developed hyperplastic nodules in the liver. Seven rats in the test group and eight in the control developed testicular tumors, and one rat in the treated group, and none in the control had neoplasms of the spleen. These results were not statistically significant. There were no significant differences in the incidences of neoplasms reported for either the treated test group or the control group. Under the procedures used, Oxyquinoline was judged to be noncarcinogenic to the male or female rats.

In 2-year NTP (1985) feeding studies with diets containing 1500 or 3000 ppm (0.15% or 0.3%). Oxyquinoline were performed using 50 male and 50 female F344/N rats. Mortality of animals consuming the test diet was not significantly greater than controls. Mean body weights for treated animals were lower than body weights of the untreated control animals. No compound-related lesions were observed in the test animals at necropsy.

Fifty male and 50 female $B6C3F_1$ strain mice were fed diets containing either 1500 or 3000 ppm (0.15% or 0.3%) Oxyquinoline for 2 years. Survival for both sexes was comparable to survival of untreated control animals. The mean body weights, for both sexes at both doses, were lower than body weights of control

animals. No compound-related lesions were noted in any animals at necropsy (NTP 1985).

Boyland (1987), in an article concerning acceptable levels of tumor promotor, listed Oxyquinoline as a tumor promoter in the category of chelating agents. The International Agency for Research on Cancer (1987) concluded that the evidence is inadequate to determine the carcinogenicity of Oxyquinoline in animals.

Ashby and Paton (1995) included Oxyquinoline in their list of chemicals that gave no evidence of carcinogenicity in mouse/rat NTP bioassays, but possessed structural alerts to genetic toxicity and were reported to be mutagenic in the Ames assay.

Eastin et al. (1998) described the NTP program's evaluation of genetically altered mice (e.g., Tg mice) as predictive models for identifying carcinogens. Oxyquinoline was studied by NTP as an example of a chemical for which there is genotoxicity in some systems, but not others, and which is apparently not carcinogenic. A Tg.AC mouse line was produced in FVB/N mice by pronuclear injection of a v-Ha-*ras* transgene linked to a fetal ζ-globin promoter and an simian virus 40 (SV40) polyadenine/splice sequence. The authors considered Tg.AC mice essentially already tumor-initiated. A $p53^{def}$ mouse line with one inactivated and one wild-type *p*53 allele were also used. In these mice, the authors considered that the chance of a single mutation leading to loss of *p*53 activity or gain transforming ability was increased.

Oxyquinoline was given topically at 0 and 225 mg/kg 5 times per week for the Tg.AC mice and at 0 and 3000 ppm in the feed of $p53^{def}$ mice (7 days per week for 24 consecutive weeks). No increased incidences of neoplasias resulted from either the topical exposure of Tg.AC mice to Oxyquinoline or feeding of Oxyquinoline to $p53^{def}$ mice (Eastin et al. 1998).

Yamamoto et al. (1998) conducted studies aimed at validation of transgenic (Tg) mice carrying the human prototype c-Ha-*ras* gene as a model for rapid carcinogenicity testing. In these mice, five to six copies of the human c-Ha-*ras* gene are integrated into the genome of each Tg mouse. Oxyquinoline was chosen to be evaluated in this system because it was considered a noncarcinogen, yet was positive in Ames tests. Tg mice were fed Oxyquinoline at 1500 or 3000 ppm for 24 weeks. There was no rapid tumor response in the Tg mice to Oxyquinoline. All but 1 of 17 carcinogens that were genotoxic gave a positive rapid tumor response. All but one of six carcinogens that were not genotoxic gave a positive rapid tumor response.

CLINICAL ASSESSMENT OF SAFETY

Human Repeated Insult Patch Test

Oxyquinoline

TKL Research, Inc. (2000) conducted a repeated insult patch test of Oxyquinoline, 1% in petrolatum. The target was 200 volunteer subjects with normal skin to complete the study conducted over a 6-week period, including induction, rest, and challenge phases. There were 227 individuals enrolled of whom 193 completed the study. Nine consecutive applications of 0.2 g of test material under occlusive patches were made to the back of each subject. Subjects removed the patches at 24 h after application. The site of application was evaluated at 48 h (except individuals who received patches on a Friday were evaluated at 72 h), and a new patch applied. This continued for nine cycles. After a 10 to 15-day rest period, a challenge patch was applied to an area not previously exposed to the test material. Again, patches were removed at 24 h. The challenge sites were evaluated at 48 and 72 h.

Results were reported on a scale of "−" to "+ + +" in five categories: no reaction; minimal or doubtful reaction; definite erythema/no edema; definite erythema and edema; and definite erythema and edema, with vesiculation. One individual exhibited a minimal or doubtful response (appearance only slightly different from surrounding skin) at each of the induction readings, but no reaction to the challenge patch. No other individual had any reaction, either during induction or challenge. The authors considered that there was no evidence of sensitization under the conditions of the study (TKL Research, Inc. 2000).

SUMMARY

Oxyquinoline is a heterocyclic phenol and Oxyquinoline Sulfate is its salt, both of which are described as cosmetic biocides for use in cosmetic formulations. A handful of uses are currently reported to FDA by industry, but industry reports to CIR indicate no use. In Europe, Oxyquinoline and Oxyquinoline Sulfate are accepted for use as stabilizers for hydrogen peroxide in rinse-off and leave-on hair care preparations, with concentration limitations.

Oxyquinoline is metabolized and excreted in the urine as glucuronides. The acute oral LD_{50} toxicity in rats was 1.2 g/kg. The interperitoneal LD_{50} in mice was 0.48 g/kg. In subchronic studies no deaths occurred in groups of five male and five female rats at five doses up to 12,000 ppm or in five male and five female mice up to doses of 6000 ppm. Loss of weight, as compared to groups of five nontreated male and female control groups occurred at doses of 12,000 ppm for males and 6000 and 12,000 for females. Male mice lost weight at the lowest test dose of 400 ppm, and in females, at the highest dose of 6000 ppm. Solid 100% Oxyquinoline was mildly irritating to rabbit skin. A 100-mg dose of Oxyquinoline was only slightly irritating to the eye.

Oxyquinoline and Oxyquinoline Sulfate were genotoxic in certain *Salmonella typhimirium* strains with metabolic activation and in a mouse lymphoma assay. There was some evidence of increased chromosome aberrations in an in vitro study, and an increase in sister-chromatid exchanges (but not chromosome aberrations) in rats treated with Oxyquinoline, but no genotoxicity was found in a *Drosophilia* sex-linked recessive lethal test, mouse bone marrow micronucleus test, a rat bone marrow and hepatocyte micronucleus test, and unscheduled DNA synthesis in rat hepatocytes. Oxyquinoline did bind to DNA in the presence of liver enzymes.

Oxyquinoline was noncarcinogenic in several rodent feeding studies. The International Agency for Research on Cancer concluded that the existing evidence is inadequate to determine carcinogenicity in animals. Recent studies using genetically altered mice, in one case carrying the human c-Ha-*ras* gene, suggested that Oxyquinoline was not carcinogenic.

DISCUSSION

In its earlier safety assessment of these ingredients, the CIR Expert Panel had concluded that the available data were insufficient to support their safety in cosmetics. The Panel notes that Oxyquinoline binds to DNA and is mutagenic in some assay systems. The CIR Expert Panel concurs with the position of the Environmental Protection Agency that bacterial mutagenic assay systems are not appropriate for assessing the mutagenic potential of microbiocides in mammalian systems. The prevalence of data from mammalian genotoxicity test systems indicates no genotoxicity. In addition, animal carcinogenicity tests have uniformly been negative. Recent use of genetically altered mice in tests to evaluate carcinogenicity have found that Oxyquinoline is not carcinogenic. Although the Panel recognizes that the International Agency for Reasearch on Cancer stated in 1987 that the available data were inadequate to determine the carcinogenicity of Oxyquinoline in animals, the data now appear sufficient to determine that Oxyquinoline is not a carcinogen in test animals.

The available clinical data demonstrate that Oxyquinoline is neither an irritant nor a sensitizer when tested at 1% in petrolatum.

The Panel was concerned with the absence of impurities data and information on the extent of skin penetration or its surrogate, the octanol/water partition coefficient. Oxyquinoline is virtually insoluble in water, suggesting that skin penetration is unlikely. Oxyquinoline Sulfate, however, is soluble in water and information as to its skin penetration is lacking. To some extent, the absence of any carcinogenic effect when Oxyquinoline was applied topically to mice is reassuring. This finding, however, does not rule out systemic effects of absorbed Oxyquinoline Sulfate. During the discussion, it was emphasized that the likely intended use of this ingredient in cosmetics is as a stabilizer for hydrogen peroxide in hair care cosmetic products. Even if there were skin absorption, given the safety test data that are available for Oxyquinoline, it is unlikely that there would be any systemic toxicity from such low concentrations in hydrogen peroxide containing hair care cosmetic products.

The Panel recognizes that use as a stabilizer for hydrogen peroxide in hair care cosmetic products is approved by use in the European Union for leave-on products at $\leq$0.03% and for rinse-offs at $\leq$0.3%, but was not clear regarding the basis for that finding. The available data demonstrating the absence of irritation and sensitization at concentrations up to 1% and the use of these ingredients at concentrations of 1% or less in rinse-off hair care cosmetic products supports the safety of these ingredients as a stabilizer for hydrogen peroxide in hair care cosmetic products. The Panel concluded that Oxyquinoline and Oxyquinoline Sulfate in rinse-off hair care cosmetic products are safe in the present practices of use.

For leave-on cosmetic products, however, the Panel did not believe there were sufficient data. The data needed in order to complete the safety assessment of Oxyquinoline and Oxyquinoline Sulfate in leave-on cosmetic products are (1) UV absorption data—if significant absorption occurs, then photoirritation/photosensitization data will be needed; and (2) impurities data.

CONCLUSION

Based on the available information, the CIR Expert Panel concludes that Oxyquinoline and Oxyquinoline Sulfate are safe as used as stabilizers for hydrogen peroxide in leave-on hair care cosmetic products. There are insufficient data to support the safety of Oxyquinoline and Oxyquinoline Sulfate in leave-on cosmetic products.

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