AMENDMENT TO FDA SULFONAMIDE MOIETY MEDICAMENTS: PHOTOSENSITIVITY.

[Document subtitle]

Citizen Petition

The undersigned submits this petition under **10.30** (relevant statutory sections, if known) of the (Federal Food, Drug, and Cosmetic Act or the Public Health Service Act or any other statutory provision for which authority has been delegated to the Commissioner of Food and Drugs) to request the Commissioner of Food and Drugs to **AMEND** (issue, amend, or revoke a regulation or order or take or refrain from taking any other form of administrative action).

DATE: 12/29/2023.

A. ACTION REQUESTED: Amend current designation of Photosensitivity involving sulfonamide medicaments to New Adverse Effect of sulfonamide medicaments of: "Photosensitivity: Caution, 'Free Radical' risk".

B. STATEMENT OF GROUNDS:

Background: many medications listed in the PDR and MPR used by health care providers have a connotation of "photosensitivity" listed under adverse effects; A classic example of this is the sulfonamide known as hydrochlorothiazide (a.k.a. HCTZ). Sulfonamides (a.k.a. sulfa) are used throughout this communication due to their chemistry. By using it and other sulfonamides, in conjunction with "laws of nature" (Biology, Chemistry, Physics and others) one can have a better understanding of the overall process.

Medically speaking, "Photosensitivity" more often than not, is translated into "skin sensitivity" and thus the prevailing thought is for one to be careful in sunlight. This is a misleading interpretation, which will be demonstrated in the following communication. By bringing to light the interplay between various disciplines (such as the pre-medical and post graduate pre-medical fields) with medicine, one can understand why the amendment is needed. This change, although minor in words, can have a significant impact on health care as a whole by decreasing; the large number of unnecessary hospital visits, ancillary use, cost, frustration and other common collateral damages we all are aware of and possibly others we are not.

Credentials: as a board-certified physician, I like others wish to abide by the oath of "do no harm" while following the "standard of care". Only by incorporating a post-graduate

pre-medical degree (Masters-Thesis Based-Chemistry) with the practice of medicine, did these findings, discussed in this amendment, become apparent.

Disclaimer: nowhere is it to be construed or perceived that this communication is to be detrimental or nefarious to any party (Person, Pharmaceutical, Profession, Medication, treatment, etc.…) in its content or thought process. Nor, whilst investigating these findings was a patient subject to any acts of unprofessionalism. As for semantics, please excuse any unprofessional flaws in scientific writing, bibliography, footnotes or other pertinent references that this author has committed by accident or omission. In citing various articles, different authors/publications/journals use various ways of nomenclature and how they were referenced.

Prior Attempts to Contact entities: Preceding the "Citizen Petition" the *Food and Drug Administration (FDA) Med Watch, was sent correspondence on the topic along with various cases this provider had seen in the past and as recent as last year. They acknowledged receiving the information and were appreciative; they went on to say if there was more information needed from the author of this communication, they would be in touch. There has been no further communication along these lines though. Unfortunate; since by addressing the topic at hand-patients submitted to them improved significantly.* Similarly, there has been little to no interest by the pharmaceutical industry for unknown reasons. Attempts to publish this in various journals has similarly failed as well. The reason(s) why is not known, but possibly due to the interplay of the multiple disciplines working in concert.

Definitions, Pre-Medical Sciences and Medicine.

Definition:

> "Photosensitivity 1. sensitivity or responsiveness to light. 2. Medicine, an abnormal heightened response, especially of the skin to sunlight or ultraviolet radiation caused by certain disorders or chemicals and characterized by toxic or allergic reaction."[1]. The adjective of Photosensitivity is Photosensitive, which by definition is "reactive to light."[2]. *More often than not, in the field of medicine, the terms apply to the skin. Unfortunate as a result, since one tends to focus on the skin, subsequently they do not realize that other organs can be affected*. Further, the definition does not take into account how chemicals in this regard undergo transformation to result in that "heightened response". This communication addresses the particulars of what "photosensitivity" is in terms of medicine, that the references used by those in and out of health care have not; for instance, using the premedical sciences to explain UVA/B absorption spectra of various medications. It is synonymous to understanding the "Krebs cycle" discussed in Biochemistry; only by grasping the particulars does one know how all of the parts interact resulting in the big picture.

[1] The American Heritage Dictionary of the English Language. Fifth Ed. Copyright 2016. ISBN 978-0-544-45445-3. Houghton Mifflin Harcourt Publishing CO., 222 Berkly Str., Boston, MA. 02116. Page 1329.

[2] Oxford Dictionary of Current English. Oxford University Press, Oxford, New York. ISBN 0-19-19—860233-2. 1998. Page 670.

"Free Radical", a noun, chemistry "atom or a group of atoms with one or more unpaired electrons"[3].
Other definitions/terminology involves electronic transitions and the ultraviolet/visible (UV/VIS) spectral absorptions. Both of these diagrams are depicted in the following:

In order to Understand the Various Electronic Transitions of the Photosensitivity Medicaments, and therefore their Respective Absorbance/Peaks/Meanings, one must first look at the each of the Components:

i. *The Sulfate Group (S02), a chromophore having both a pi to pi anti-bond = π--->π* and non-bonding to pi anti-bonding = nb--->π* transitions.*

ii. *The Benzene Group, a chromophore, π--->π* transitions.*

iii. *The Amine affect on the Benzene group (auxochrome nb--->π* effect inducing a chromophore π--->π*) transitions.*

iv. *The Sulfonamide Group, R-SO2-NR'R" a chromophore with both π--->π* and nb--->π* transitions.*

v. *The Sulfonamide/Sulfa Medication Complex as a Whole, π--->π* and nb--->π* transitions.*

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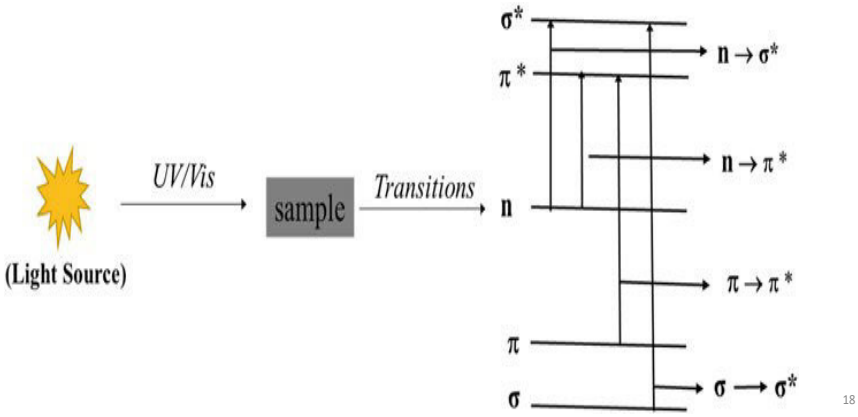
[3] Oxford Dictionary of Current English. Oxford University Press, Oxford, New York. ISBN 0-19-19—860233-2. 1998. Page 348.

Effect of uv/vis radiation on electronic transitions which includes sunlight.

Khan, Shahid & Khan, Sher & Khan, Latif & Farooq, Aliya & Akhtar, Kalsoom & Asiri, Abdullah M.. (2018). Fourier Transform Infrared Spectroscopy: Fundamentals and Application in Functional Groups and Nanomaterials Characterization. 10.1007/978 -3-319-92955-2_9.



Pre-Medical Sciences: *the following falls under common knowledge in the fields of Biology, Chemistry as well as various aspects of Physics (previously stated as some of "the laws of nature"). It is not meant to be a didactic but to emphasize common knowledge in those individuals who fulfilled the pre-medial requirements prior to their medical training. The reader is directed to the bibliography for further information on the specific topic they may have questions on (see Libre Texts Libraries: Chemistry, Physics and others-for the specific topics. Use search bar and type; for example, if one wants to see how hyperconjugation affects the free radical stability they type: Hyperconjugation/free radicals chemlibrtexts. Note: this information downloaded via the internet). For those who do not have the aforementioned knowledge, they may wish to speak with those they know who do.*

The sulfonamide moiety known as R-SO2-NR'R" (and hereby known as moiety in this communication): has two double bonds (a.k.a.: double bond, =) between the sulfur (S) and two oxygens (O), ergo 2 @ S=O; and two single bonds (a.k.a. single bond, -), one to the N (Nitrogen), thus S-N, and the other to a R group (usually a carbon) as S-R, respectively.

The R groups also have an effect on the moiety, for they too can have photosensitivity properties and thereby generate "free radicals" as well.

The sulfur atom is hybridized such that it can form six (6) bonds (two double bonds and four single bonds in the sulfonamide moiety) due to its ability to hybridize (form a sp3d2 hybridized bond). This leaves three (3) empty d orbits (out of a total of five [5]) on S available for other interactions with the N and O atoms. There are ten (10) total unpaired electrons on the non-bonding orbits between the O and N associated with the moiety. These electrons can undergo movement into the empty d orbits of the S. This can allow migration of electrons, which can enhance resonance (bonding of various atoms in structures), resulting in a stabilizing effect on the "free radical".

Most important in terms of this communication, the non-bonding electrons and the pi electrons can undergo movements into higher "orbits" associated with the compound when

sufficient energy is instilled in it-thus generating the "free radical". Although there are different transitions that can occur, the ones most important in the photosensitivity compounds known as sulfonamides, are both the nb--->π* and π--->π*. The "free radical" movement is in accordance with the Jablonski diagram. Due to limitations in space and scope of this communication see Alemany-Ribes M. footnote, and for those wanting a more in-depth review one can query via LibreTexts libraries in the biography as well for the Jablonski diagram and its implications.

This transition can occur with the non-bonding electrons associated with the O atoms bound to the S atom (and elsewhere in the molecule with double bonds involving the oxygen atom, both of these are known as chromophores) in the moiety due to the "stabilizing" factor just discussed-along with others to be discussed. The energy required to do this occurs in the realm of the UVA/UVB region (ultraviolet A and ultraviolet B) which is part of sunlight (as well as other sources of radiation such as artificial lighting[4]) and has been discussed by others due to their potential harmful effects-using the term UV index[5]. This region, UVA 315-400 nanometers (nm) and UVB 280-315 nm respectively, others have stated that these reactions occur into the visible range (up to 800 nm) as well[6]. UVB has been associated with non-bonding to antibonding movements of the oxygen atom electron @ 280 nm (R_2-CO, such as those outside of the sulfonamide moiety), while the UVA similar transition of the non-bonding electrons @ 340 nm on the nitrogen (R-N=N-R)[7]. Further the benzene group (also known as aryl group) also has transitions in this area of 270 nm for the π--->π*, these transitions (as will be discussed) have to do with excited vibrational movements in the Jablonski diagram; more specifically the vibrational transitions according to the chem libre texts. For instance, this involves the absorption of energy followed by movement into S2 as compared to S1 in the Jablonski diagram. Movement then occurs from S2 to S1 followed by intersystem crossing resulting in the excited triplet "free radical". See the following diagram:

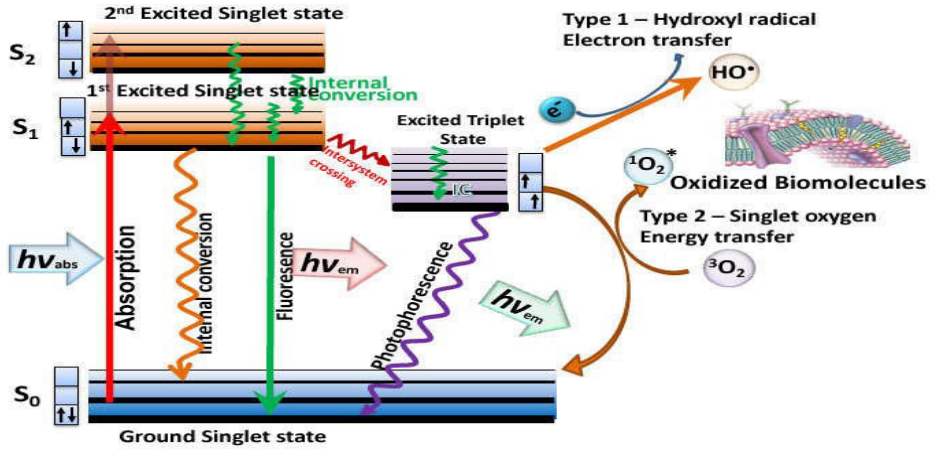
[4] Kowalska J, Rok J, Rzepka Z, Wrześniok D. Drug-Induced Photosensitivity-From Light and Chemistry to Biological Reactions and Clinical Symptoms. Pharmaceuticals (Basel). 2021 Jul 26;14(8):723. doi: 10.3390/ph14080723. PMID: 34451820; PMCID: PMC8401619.

[5] Heckman CJ, Liang K, Riley M. Awareness, understanding, use, and impact of the UV index: A systematic review of over two decades of international research. Prev Med. 2019 Jun; 123:71-83. doi: 10.1016/j.ypmed.2019.03.004. Epub 2019 Mar 4. PMID: 30844501; PMCID: PMC6534479.

[6] Georg Amun Hofmann and Benedikt Weber. *Drug-induced photosensitivity: culprit drugs, potential mechanisms and clinical consequences* J Dtsch Dermatol Ges. 2021 Jan; 19(1): 19–29. Published online 2021 Jan 25. doi: 10.1111/ddg.14314.

[7] Introduction to Spectroscopy. Donald L. Pavia, Gary M. Lampman, George S. Kriz, James A. Vyvyan. Table on page 362. 1305177827, 9781305177826. PP 784.

Hamblin, Michael R. (1,2,3 -author to correspond with),Abrahamse, Heidi (4). "Inorganic Salts and Antimicrobial Photodynamic Therapy: Mechanistic Conundrums? *" Molecules 2018, 23 (12), 3190. Published 3 December 2018.*
1. Wellman Center for Photomedicine, Massachusetts General Hospital, Boston, MA 02114, USA.
2. Department of Dermatology, Harvard Medical School, Boston, MA 02115, USA
3. Harvard -MIT Division of Health Sciences and Technology, Cambridge, MA 02139, USA
4. Laser Research Centre, Faculty of Health Science, University of Johannesburg, Johannesburg, Doornfontein 2028, South Africa.



Note: these values are not set in gold, they may vary depending on the R groups associated with them for they can cause shifts in wavelength and absorption, thus oxygen nb--->π* can be between the two listed values. Similarly; other compounds may absorb in these regions as well such as the S=O in SO_2 (to be discussed later).

Findings of this nature can explain the absorption of 270 nm for the π--->π* associated with the aryl group and 290-350 nm for the nb--->π* absorptions associated with the R-SO2-NR'R" and aryl amines (R groups bound to N). Thus, a more concise peak occurs slightly before or near 270 nm whereas a broader peak at different wavelengths occurs between 290-350 nm due to it involving the -SO2- and the aryl amine together. In both cases the peaks are of low absorption due to the forbidden singlet to triplet "free radical formation according to the Laporte rules. This is demonstrated in the following UV/VIS spectral absorption of furosemide. Peak 2 involves the aryl vibration absorption while the broader peak 1 involves the sulfonamide moiety and aryl amine absorptions.

Development of UV spectrophotometric methods and validation for estimation of furosemide in bulk and tablet dosage form by ab sorbance maxima and Area Under the Curve method Gahandule Mangal* and Banerjee S. K Advanced Quality Assurance Technique Department, Vishal Institute of Pharmaceutical Education and Research, Ale, Indi International Journal of Advances in Pharmaceutics ISSN: 2320 –4923; DOI: 10.7439/ijap Volume 5 Issue 6 [2016] Journal home page: http://ssjournals.com/index.php/ijap

oncentration: 5,10,15,20,25 µg/ml.

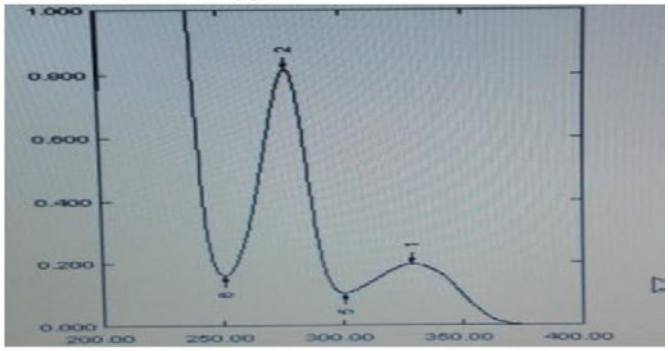


Figure 3: Standard solution of 15µg/ml

Furosemide
Molecular Formula: $C_{12}H_{11}ClN_2O_5S$
Average mass: 330.744 Da
Chemical name:4-chloro-2-[(furan-2-ylmethyl] amino]-5-sulfamoylbenzoic acid

This technique is complementary to fluorescence spectroscopy, in that fluorescence deals with transitions from the excited state to the ground state, while absorption measures transitions from the ground state to the excited state.[11]. Structure and formula from "drugsdetails.com/furosemide" downloaded from internet.

Other factors can influence the absorption as well, for instance stabilizing factors of the "free radical". Some of these factors involve: hyperconjugation, resonance and non-bonding electrons (common knowledge in chemistry). This occurs by allowing movement of electrons, in a supportive manner, to the area vacated by the π--->π* and the nb--->π* electrons. An example of this are the nonbonding electrons on the N which can bond with the empty d orbits on the S. Evidence in support of the bonding that non-bonding electron in N can do with S, is the Trisilylamine-N($[SiH_3]$)$_3$ molecule which has a planar structure.

> *This is important since it reveals that the non-bonding electrons of the N can back bond into the empty d orbit of the Si (Silicon)[8]. This explains why ammonia (NH_3) is trigonal pyramid, but Trisilylamine is trigonal planar. Given that the S has empty d orbits as well as the Si due to its hybridization (as discussed earlier) it too can back bond with the non-bonding electrons on the N (both are in the same period and block of the periodic table and therefore react similar). Thus, this aspect of the sulfonamide moiety can be planar with the N and two Os all being in the same plane. This will allow resonance as well as hyperconjugation, which can have an effect on the UVB/A absorptions of the various sulfonamide compounds along with increasing their stability and thus half-life (a.k.a. t1/2).*

Some movements of electrons may occur but only "weakly" and thus they are referred to as "forbidden". For instance, non-bonding electrons on the O in the S=O of the sulfonamide moiety can do this as well as those on the N. Thus, the amplitude of this "forbidden" (or weakly allowed) peak is low and can be broad (more to follow on this shortly in the singlet to triplet "free radical" discussion). Other considerations complexing the absorptions are the R groups bound to the moiety since they may alter the absorptions

[8] The Molecular Structure of Trisilylamine $(SiH_3)_3N^{1,2}$. Kenneth Hedberg. *Journal of the American Chemical Society* **1955** *77* (24), 6491-6492. DOI: 10.1021/ja01629a015

as a result of their electron density. Depending on whether they donate or accept electrons, this can influence lambda max (maximum absorption of the UVA/B wavelength shift and its intensity [molar absorption coefficient] in this case). These are known as auxochromes- see footnote six and bibliography for more details.

Examples of this; Furosemide has the following absorptions 288 & 276 nm (UVB) and **UVA** of **336 nm** in 95% ethanol[9]. While Hydrochlorothiazide, a different sulfonamide moiety compound, has the **UVA**/B range of **317 nm** / 271 nm respectively[10]. The non-medicine sulfanilamide compound has absorption max absorption at the non-UVA/UVB wavelength of 257 NM and a very close to **UVA** of **313 nm**[11]. Although all three have the sulfonamide moiety they have different R groups which in turn affects the maximum absorption in the UVA/B spectrum (tabular data will follow).

Sulfur dioxide (SO_2) has three absorptions in the UV spectrum. They are: (1) very weak absorption in the 340 nm to 390 nm range; (2) semi-strong absorption in the 250 nm to 320 nm range; and (3) strong absorption in the 190 nm to 230 nm range[12]. Most important in terms of this communication is Number (2) which falls in the realm of the oxygen's nb--->π* orbit electrons, based on foot note 6. Although SO_2 is a different molecule verse R-SO2-NR'R" they both have non-bonding electrons on the oxygen (those on O in S=O) and thus abide by similar laws of electron transition in the UV/VIS range. See following diagram. Note: **the non-bonding to pi anti-bonding = nb--->π* 250 nm to 320 nm range** and 190 nm to 230 nm range **pi to pi anti-bond = π--->π***; and other connotations by Dr. Webb using the preceding discussion, ***not the author of the said article***.

[9] O'Neil, M.J. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. Cambridge, UK: Royal Society of Chemistry, 2013.

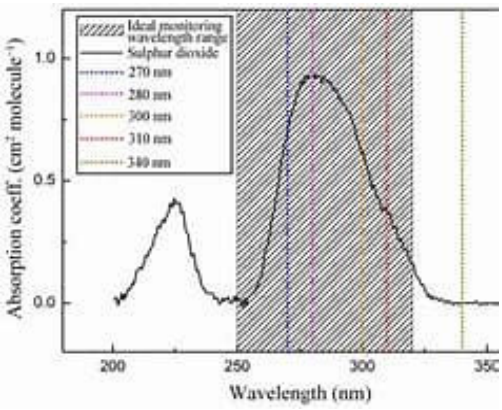
[10] O'Neil, M.J. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. Cambridge, UK: Royal Society of Chemistry, 2013., p. 885

[11] *Budavari, S. (ed.). The Merck Index - Encyclopedia of Chemicals, Drugs and Biologicals. Rahway, NJ: Merck and Co., Inc., 1989., p. 1409.*

[12] Using Multispectral Imaging to Reveal the Relationship between UV Absorbance and Sulphur Dioxide Concentration by Keru Lu 1, Zhilin Li 1,2 and Man Sing Wong 1, *ORCID 1 Department of Land Surveying and Geo-Informatics, The Hong Kong Polytechnic University, 181 Chatham Road South, Kowloon, Hong Kong 2 Faculty of Geosciences and Environment Engineering, Southwest Jiao Tong University, Chengdu 611756, China * Author to whom correspondence should be addressed. Sustainability 2023, 15(1), 138; https://doi.org/10.3390/su15010138 University, Chengdu 611756, China Sustainability 2023, *15*(1), 138; https://doi.org/10.3390/su15010138

Sulfur Dioxide (SO2; O=S=O; has SP2 Hybridization with Non-Bonding Electrons on O [8 total] and S [2 total]) Similar to Sulfonamide/Sulfa Absorption.

Sulfur dioxide (SO_2) has three absorptions in the UV spectrum. They are: (1) very weak absorption in the 340 nm to 390 nm range; (2) semi-strong absorption in the non-bonding to pi anti-bonding = nb--->π* 250 nm to 320 nm range and (3) strong absorption in the 190 nm to 230 nm range pi to pi anti-bond = π--->π*. Most important in terms of this communication is Number (2) which falls in the realm of the oxygen's non-bonding to pi-antibonding orbit, based on foot note 6. Although SO_2 is different from R-SO2-NR'R" they both have non-bonding electrons on the oxygen and thus abide by similar laws of electron transition in the UV/VIS range.



Using Multispectral Imaging to Reveal the Relationship between UV Absorbance and Sulphur Dioxide Concentration by Keru Lu 1, Zhilin Li 1,2 and Man Sing Wong 1, *ORCID 1 Department of Land Surveying and Geo -Informatics, The Hong Kong Polytechnic University, 181 Chatham Road South, Kowloon, Hong Kong 2 Faculty of Geosciences and Environment Engineering, Southwest Jiao Tong University, Chengdu 611756, China * Author to whom correspondence should be addressed. Sustainability 2023, 15(1), 138; https://doi.org/10.3390/su15010138 University, Chengdu 611756, China Sustainability 2023, *15*(1), 138;https://doi.org/10.3390/su15010138

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Related compounds to the sulfonamide moiety (R-SO2-R'R") and others having C=O chromophores (both are present in medicaments concerning this communication) have the following UV/VIS absorptions: Benzaldehyde (C6H5-CO-H) Max absorption (cyclohexane) followed by molar absorption coefficients: 241 nm (log e= 4.15); 247 nm shoulder (log e = 4.06); 277.5 nm (log e = 3.08); 287 nm shoulder (log e = 3.00)[13], Benzyl amine (NH2CH2C6H5) UV: 266[14], and the Sulfanilamide (NH2C6H4SO2NH2) MAX ABSORPTION: 257 NM, 313 NM[15]. Remember: π--->π* (near 270 nm [nano meters] for aryl group vibration); and non-bonding to pi anti-bonding = nb--->π* (290-350 nm). Tabularly the preceding absorptions are:

Name	UVB 280-315 nm	UVA 315-400 nm
Chromophore	π--->π*	nb--->π*
1. Sulfur Dioxide	-	250-350
2. Benzaldehyde	277.5-278	-
3. Benzylamine	266	-
4. Sulfanilamide	-	313
5. Hydrochlorothiazide	271	317

[13] *Weast, R.C. (ed.). Handbook of Chemistry and Physics. 60th ed. Boca Raton, Florida: CRC Press Inc., 1979., p. C-140.*

[14] (Sadtler Research Laboratories Spectral Collection) *Lide, D.R., G.W.A. Milne (eds.). Handbook of Data on Organic Compounds. Volume I. 3rd ed. CRC Press, Inc. Boca Raton F L. 1994., p. V1: 1008*

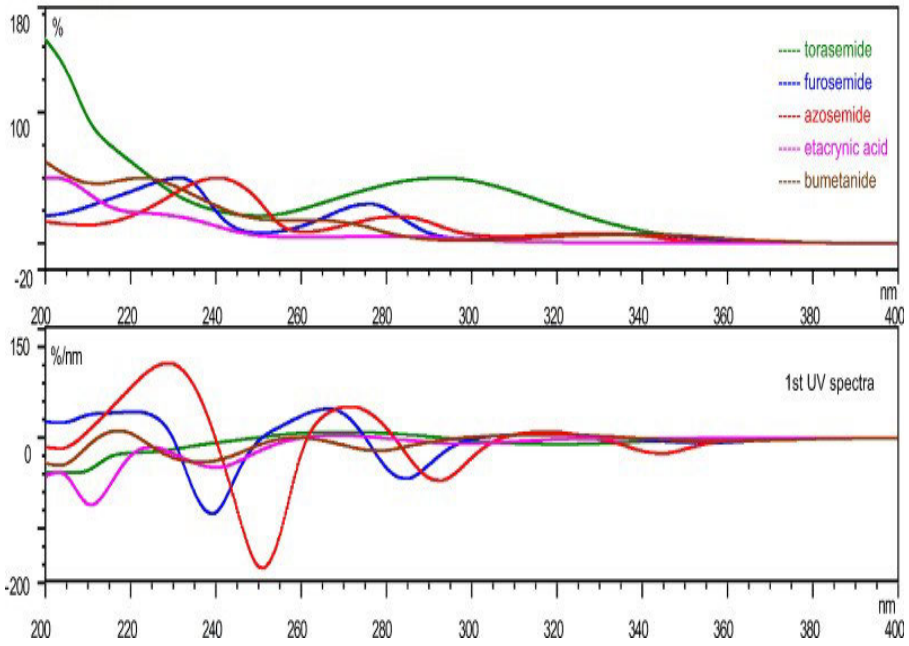
[15] *Budavari, S. (ed.). The Merck Index - Encyclopedia of Chemicals, Drugs and Biologicals. Rahway, NJ: Merck and Co., Inc., 1989., p. 1409*

6. Furosemide 276-288 336

Using some of the "laws of nature" (chemistry and quantum mechanics); Beer-Lambert, Laporte, and Spin Coupling-the broad and low amplitude peaks of various sulfonamides can be associated with what are known as "forbidden transitions" (discussed earlier). Which others have said "In, such cases the singlet-triplet absorption spectra will be exceedingly weak, and consequently difficult to observe"[16]. Forbidden transitions, although listed as "forbidden" can still occur; they occur but not to the extent of other transitions as listed in chem libre texts in the bibliography. For here they entail a change of the dipole of an electron, from the singlet to triplet "free radical", in accordance with the Laporte rules *(g--->u).*

This can explain the peaks in the following absorption loop diuretic spectra. Note: ethacrynic acid is a non-sulfonamide and it does not absorb in the aforementioned areas.

Chen F, Fang B, Li P, Wang S. Simultaneous determination of five diuretic drugs using quantitative analysis of multiple components by a single marker. BMC Chemistry. 2021 Jun;15(1):39. DOI: 10.1186/s13065 -021-00764-z. PMID: 34108013; PMCID: PMC8191180.



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In short, by using the preceding information; absorption of sulfonamides and aryl amines at these wavelengths (near or above 300 nm and into the UVA range) undergo the "forbidden" transformation (peaks with low amplitude and absorption) of singlet "free radical" to triplet "free radical" conversion. Similarly, the aryl groups involve a

[16] **The effect of environment on singlet-triplet transitions of organic molecules.** D. F. Evans. *Proc. R. Soc. Lond. A*25555–63. Published:22 March 1960 https://doi.org/10.1098/rspa.1960.0049.

forbidden transition by involving the vibrational transformation of the pi orbits in the lower UVB range, thus resulting in its "free radical" transformation. This occurs on a regular basis when exposed to radiation such as sunlight.

To say with certainty what these transitions involve is difficult other than saying it is in the realm of nb--->π* wavelength for the oxygen atoms on and outside of the moiety. For instance, O atoms elsewhere on the molecule can transition at 280 nm while the ones associated with the sulfonamide moiety do so at longer wavelength (300 nm and above in the UVA range). None-the-less this correlation can explain why the UVA/B spectral region is important in the formation of "free radicals" previously discussed[17]. Although it is beyond the scope of this communication, the carbonyl and sulfonyl oxygen's non-bonding electrons are influenced by different auxochromes (such as amines bound to the S atom in the moiety) which can also influence where the peaks and their amplitudes fall within the UVA/B spectrum. Normally the life span of these unpaired electron transitions (known as a singlet) has a relatively short period on the order of nano to Pico seconds (10^{-9} to 10^{-12}): using the Jablonski diagram, however, intersystem crossing allows a triplet form of the "free radical" to be formed from the singlet. The triplet form has a much longer life span-milli to nano seconds (10^{-3} to 10^{-9})[18]. The triplet form can interact with other molecules (in the body) to produce ROS (Reactive Oxygen Species) via transfer of an electron (ROS type one [ROS I] generating O_2^-, -OH, and H_2O_2) as well as ROS type II, by way of an energy transfer, resulting in singlet oxygen ($^1O_2$) from triplet oxygen ($^3O_2$)- see Alemany-Ribes reference below.

> ***"In view of this, it is here that the sulfonamide moiety medicaments exert its deleterious free radical effect. For its "forbidden" triplet "free radical" can range throughout the body due to the longer t1/2, thus potentially generating ROS not just at its target destination but also at various sites along its way".***

ROS compounds are very reactive and also destructive. For instance, they are used in PDT (Photodynamic Therapy) to target and destroy cancer cells amongst other uses. It can do this by damaging their cell walls, RNA and DNA and other component of the tumor via their oxidative (or reducing properties) in their quest to bond with other electrons at these sites[19].

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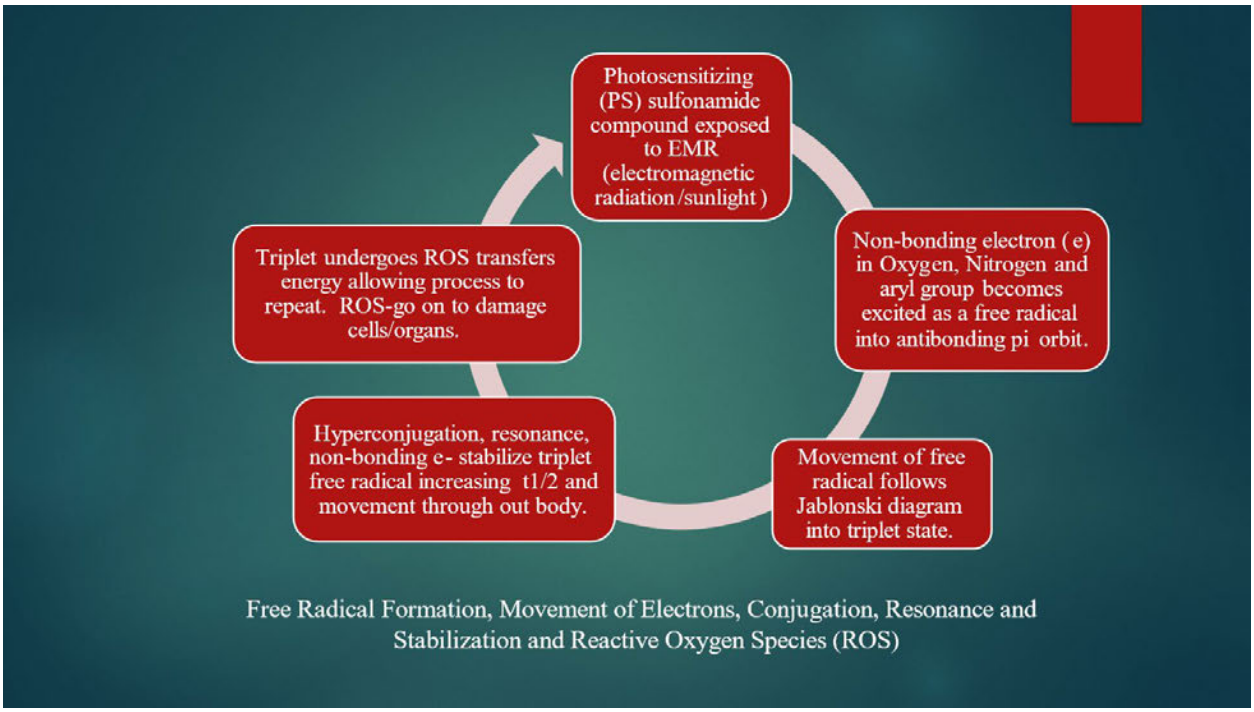
[17]Georg Amun Hofmann and Benedikt Weber. *Drug-induced photosensitivity: culprit drugs, potential mechanisms and clinical consequences* J Dtsch Dermatol Ges. 2021 Jan; 19(1): 19–29. Published online 2021 Jan 25. doi: 10.1111/ddg.14314.

[18] Hamblin, Michael R. (1,2,3-author to correspond with), Abrahamse, Heidi (4). "Inorganic Salts and Antimicrobial Photodynamic Therapy: Mechanistic Conundrums?" *Molecules 2018, 23 (12), 3190. Published 3 December 2018.* 1. Wellman Center for Photomedicine, Massachusetts General Hospital, Boston, MA 02114, USA. 2. Department of Dermatology, Harvard Medical School, Boston, MA 02115, USA 3. Harvard-MIT Division of Health Sciences and Technology, Cambridge, MA 02139, USA 4. Laser Research Centre, Faculty of Health Science, University of Johannesburg, Johannesburg, Doornfontein 2028, South Africa.

[19] Alemany-Ribes M[1], García-Díaz M[1], Acedo P[3], Agut M[1], Nonill S[1], Sagristá ML[2], Mora M[2], Cañete M[3], Villanueva A[3], Stockert JC[3] and Semino CE[1*]. " Why Not Introducing the Third Dimension in Photodynamic Therapy Research?" *J Anal Bioanal Tech S1:004, 2013.* Access [1]IQS School of Engineering, Ramon Lull

Summary: the following diagram reveals the sequence thus far.



Medicine: as a health care provider, during exams I ask the patient the open-ended question of "…how is your skin doing?". Often those on sulfonamide medicaments respond that they have to be careful with sun exposure. When asked why, some cite it says to on the package insert, others state their skin is sensitive (has darkened, burns easily, vesicles may develop on the left arm/leg as the driver in a vehicle in this country, these are just some of the symptoms). When asked how long these issues have occurred, often the reply is around the time they started the sulfonamide. Others may say with a new occupation such as an arc welder while on the moiety or after traveling to a "sunbelt" region from less sunny areas. This darkening effect on the skin makes sense due to the increased melanin production to offset the untoward effects, in this case, of the sulfonamide moiety. More specifically:

> *"UV rays induce melanin production in the skin, which from a cosmetic point of view, is problematic. Reactive oxygen species (ROS) generated in the skin upon UV irradiation are thought to be responsible for melanin production."*[20].

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[20] Shiota, Kanako, Hama, Susumu, Yoshitomi, Toru, Nagasaki, Yukio, Kogure, Kentaro. "Prevention of UV-Induced Melanin Production by Accumulation of Redox Nanoparticles in the Epidermal Layer via Iontophoresis". *Biol Pharm Bull. 2017;40(6):941-944.*

This is further amplified by the use of a sulfonamide medicament which promotes ROS as well as has just been discussed. It explains why patients who are placed on the moiety show a darkening of their skin over time (due to increased melanin). Thus, use of treatments like this in patients already at risk for skin issues (Psoriasis, Lupus and others) encourages worsening of their conditions.

> *In fact, some have found sulfonamides (amongst others) promote the "Koebner Phenomena" in certain individuals, this may explain why individuals wearing "Unna Boots", compression stockings or other constrictive clothing can accentuate the drug induced lichen planus in these areas*[21].

Unfortunately, lichen planus can present in similar fashion to stasis dermatitis and as a result it is treated in such fashion which often makes the former of the two worse. This in turn is followed by escalating the treatment due to the thought process that the stasis dermatitis is getting worse. By discontinuing the sulfonamide and using a non-sulfonamide alternative to treat the disease, both the stasis dermatitis and lichen planus improve as has been discussed in cases submitted to FDA MedWatch by this provider. In one case the patient lost forty (40) pounds in thirty (30) days when the change was made. The patient at the time was on furosemide of 40 mg a day prior to the change to the non-sulfonamide loop diuretic.

Similarly, the darker one's complexion, the more radiation is absorbed. This is known as "black body absorption" and is well known in the fields of chemistry and physics. It is important in terms of this communication due to its effect on "free radical" formation. More specifically individuals with a darker complexion while on the sulfonamide moiety compound are more likely to generate ROS due to this. People of "color" (a relative term, can include any individual in which the skin takes on a darker complexion, but often refers to minorities) tend to be on these compounds due to genetic factors that predispose them to ill effects of the "western diet", such as salt-contributing to hypertension.

Associated with "black body" absorption is the equally well known "black body radiation" effect; which in the field of chemistry and physics involves emitting radiation from a "black body". Ironically this concept helps to explain why "people of color" have a higher core temperature than their Caucasian counter parts (all parties in good health and not taking medications per the article)[22]. Although that author attributes the temperature elevation to genetics it does not explain why Caucasian males have a lower temperature than African American females in the article; for one would expect that the males would be more metabolically active (due to muscle) than females and thus have a higher temperature. Although, the Caucasian males due have a higher core temperature compared to Caucasian

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[21] Current Medical Diagnosis & Treatment 2022. Maxine A Papadakis, Stephen J. McPhee, Michael W. Rabow. Sixty-First Edition. A Lange medical book. McGraw Hill, New York and other locations. Copyright 2022. Page 146.

[22] K P McGann[1], G S Marion, L Camp, J G Spangler *The influence of gender and race on mean body temperature in a population of healthy older adults*. Arch Fam Med 1993 Dec;2(12): 1265-7.doi: 10.1001/archfami.2.12.1265.

females it does not appear to be "statistically significant" as compared to the African American females.

In view of this, higher core temperature correlates with more radiation absorption in the UV/VIS spectrum by the African American females (per the article there is no mention of the patients being exposed to other sources of radiation [e.g., x-rays], ergo only sunlight and artificial lighting are the environmental sources) with subsequent "black body radiation" in the infrared/thermal realm (infrared radiation results in the higher core temperature). The point here is, darker complexioned individuals absorb more UV/VIS radiation and when on a sulfonamide moiety medicament this promotes ROS, via "free radical" formation.

Unfortunately, the same ROS properties that help to destroy harmful cells (such as tumors) in the body can have the same detrimental effects on biomolecules of healthy cells as well[23]. Thus, the various organs in which these compounds are in or pass thru are at risk. This can explain why so many organs are involved especially with compounds having a long half-life (t ½) are affected. Free radicals of this harmful nature have been discussed by others outside of medicine[24] and within[25]. although the life span of the triplet free radical is still short, it is increased via resonance, hyperconjugation and non-bonding electrons discussed earlier in this communication. No longer is it on the milli- to nanosecond time line, but much longer. In doing so this allows these "radicals" to perfuse though out the body until they come to an area where they accumulate (one of the best-known long-lasting triplet free radicals is the oxygen molecule, $^3O_2$-which of course is essential to human life). For instance, HCTZ works primarily at the kidney, therefore it would concentrate there as would the "free radical" form of the HCTZ.

> *Thus, damage there (the kidneys in this case) can be reflected in such conditions as interstitial nephritis, often unfortunately diagnosed as a urinary tract infection even though work up does not show evidence of this (negative cultures for instance). This results in multiple treatments, often using antibiotics, further promoting "collateral damage" (risk of resistance, increase cost as well as other unnecessary outcomes) in the "ill fated" attempt(s) to correct.*

In view of the damage of the HCTZ "free radical", this can explain why the kidney is especially at risk. Similar outcomes can be expected in other organs where those "free radicals" concentrate (thus pancreatitis with the sulfonamide glyburide per the PDR). Of

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[23] Toxic Substance Mechanisms Volume 18, 1999 - Issue 2 *PHOTOTOXICITY INDUCED BY 1O2 GENERATION DURING THE PHOTODEGRADATION OF SOME DIURETIC DRUGS.* Franklin Vargas, Hisbeth Mendez, Julio Sequera, Jenny Rojas, German Fraile, Mait Velasquez. Pages 53-65 | Published online: 16 Jul 2015.

[24] F Vargas[1], I Martinez Volkmar, J Sequera, H Mendez, J Rojas, G Fraile, M Velasquez, R Medina. *Photodegradation and phototoxicity studies of furosemide. Involvement of singlet oxygen in the photoinduced hemolysis and lipid peroxidation* J Photochem Photobiol B. 1998 Mar;42(3):219-25. doi: 10.1016/s1011-1344(98)00074-8.

[25] *Antimicrobial Photosensitive Reactions.* Snejina G. Vassileva, MD; Grisha Mateev, M; Lawrence Charles Parish, MD. ARCH INTERNAL MED/VOL 158, OCT 12, 1998. PP 1993-2000, and references there in.

note: HCTZ has two sulfonamide groups as compared to others such as furosemide. Ergo, twice the risk of free radical formation vs compounds having only one such moiety and may explain why it is often associated with photosensitivity in various publications.
These findings "bridge the gap", that others have suggested, that certain patients reacting to them (sulfonamides), are just more reactive to various medicaments. Such is the case with a publication by Dr. Brian Strom and others in the NEJM 2003[26]. The article focuses on allergies, and unless there is a type I-IV hypersensitivity or other serious reaction (for instance severe leukopenia) then one can still use the medicament. Unfortunately, there is no mention in the article about the chemistry of the sulfonamide moiety. More specifically how "free radicals" can be generated by them.

> *This is not uncommon: for many of us (myself included, for what it is worth), tend to focus on the medical aspects in patients, whilst not using "all of our (pre-medical) knowledge.*

Many health care providers cite Dr. Strom's article as a reason for the continued use of these medicament(s) even though individuals are showing untoward effects associated with them such as "photosensitivity". This in turn results in third parties (for instance insurance companies) not allowing alternative treatments that would correct for this, thereby compounding the situation when it could have been corrected. In this regard the patient is forced to pay out of pocket for the alternative treatments to avoid that aftermath. Anecdotally that was the case in one patient seen by the author. Not only did they improve in terms of signs (decreased skin complexion) and symptoms (less flares of asthma) but so did their lab work (resolution of pyuria for example).
Others have said that patients of this nature often improve using non-antibiotic sulfonamides (like furosemide), when hospitalized for such things as congestive heart failure (CHF) with bilateral lower extremity edema. Thus, their outpatient failure has to be due to other factors (like non-adherence to the provider recommendations). However, what is not realized in this situation is that "all cells" in the body (and thus organs) are at risk for damage due to "free radicals". Therefore, the gastrointestinal tract (an organ) does not absorb oral medications as well. By giving medications, intravascularly in the hospital, this is overcome-and thus the patient starts improving and rapidly. Prior to discharge though, individuals are transitioned back to oral agents and the process repeats; i.e., malabsorption of the principal medication thereby resulting in the resumption of edema which again becomes evident over time. This requires additional measures and or hospitalizations to overcome; consequently, driving up health care costs while also introducing other factors that further complicate the patient's medical history.
It's not just the primary organ that is affected, patients on these medications presenting in CHF can have multiple organs contributing to it-not just the heart but: kidneys, lungs, skin, and gastrointestinal tract amongst others. By eliminating agents that generate "free radicals" which percolate though out the body, all organs improve as does the CHF, like

[26] Dr. Brian Strom and others (due to space). *Absence of Cross Reactivity between Sulfonamide Antibiotic and Sulfonamide Nonantibiotics* October 23, 2003 N Engl J Med 2003; 349:1628-1635. DOI: 10.1056/NEJMoa022963.

the patient already discussed who lost 40 pounds in thirty days. By all the organs working in concert this can explain the rapid and dramatic weight loss in such a short period of time. Ironically, some on the other hand have identified the sulfonamide-furosemide having absorption spikes. These spikes can result in varying concentrations which can have negative effects on organs-thus affecting the fluid status. As a result, they have modified how the compound is absorbed. In doing so a better steady state of the medication in the body can result, without as much untoward organ effect, all the while increasing the amount of medication absorbed thereby increasing diuresis as well[27]. *However, in doing so it will ultimately increase the concentration of the sulfonamide moiety within the body, thus increasing "free radical" formation-resulting in more damage to cells/organs which in turn causes more fluid retention by affecting the various organs as discussed*.

DISCUSSION:

Given the wide use of the sulfonamide moiety in treatments/medications, the preceding amendment communication ***"Photosensitivity: Caution, 'Free Radical' risk".*** will no doubt have a significant impact on medicine in both positive and negative ways. "A double-edged sword if you may". Examples of this would be; using the moiety in an antibiotic for a short period of time verse the same moiety diuretic for hypertension chronically. For here, it is more likely that the latter of the two examples will have deleterious effects on the body due to the effect of the "free radicals". This has been displayed in the previous diagram page 12.

There are alternatives to overcome the negative component of the "double edged sword" though. As an example; by using a medicament with a different moiety (non-sulfonamide), that still treats the initial condition that the sulfonamide moiety did, the untoward effect ("free radical") does not occur. In some patients already on the sulfonamide, if they are changed accordingly to a non-sulfonamide treatment designed to treat the initial condition of the sulfonamide agent used, one can see marked improvement in short order (since not only is the initial organ treated but multiple organs are no longer affected by the sulfonamide). Of course, this is under the pretense the new treatment does not generate "free radicals" itself or have as deleterious effects on the body that obviate their use in the first place, and that the alternative exists in the first place.

Note: in doing this one has not only treated the initial organ disease but also removed an inciting factor contributing to it and other organ dysfunction (by removal of the "free radical"). This will result in patient improvement along with decreased amounts of medicaments/treatments with time that would be needed if the moiety had not been removed.

[27]COMPOSITIONS AND METHODS FOR LOOP DURETCS WITH CONSISTENT BOAVAILABILITY (12) United States Patent Mathiowitz et al. Edith Mathiowitz, Brookline, MA (US); Bryan Laulicht, Great Neck, NY (US). US008685947B2 US 8,685,947 B2 Apr. 1, 2014.

On the other hand; sulfonamide moiety medicaments have been a staple in various chronic illnesses, especially in certain populations ***such as veterans***-many of which have CHF for example. To all of a sudden stop using them or change to alternative agents requires significant proof to do so. Is there proof of what you are saying in terms of cases? And if so, where?

Unequivocally yes! Once again, anecdotal cases have been presented to the FDA MedWatch recently and in the past. Not only did the submitted cases reveal the cause of the "free radical" formation, they also included the solutions and, in some cases, it entailed just merely stopping the offending agent. Other cases are available via, FIOA (Freedom of Information Act) at places where the author has previously worked.

CONCLUSION:

By amending the current "Photosensitivity" listing to, ***"Photosensitivity: Caution, 'Free Radical' risk".,*** using the FDA's Citizen Petition clause 21 FRC 10.30. Consumers along with providers will subsequently have more knowledge concerning adverse effects in some of the treatments they use. This in turn will have a significant impact on prescribing these medicaments in a positive way, for it will make entities pause first and think about some of the side effects, before "knee jerk" responding, to their use in various medical conditions.

This will substantially decrease patient morbidity and mortality;, whilst still allowing the oath of "do no harm" in the pursuit of providing the "standard of care", by health care providers.

Collaterally there will be a decrease in; ancillary uses, costs, frustration and other *confounding factors* contributing to health care expenses-thereby decreasing the 1.3 million emergency department visits along with the 350,000 hospital floor admissions that occur each year in this country due to adverse drug events (per the CDC recent posting). Further, pending other influences (environmental, culture, occupation…) patients may qualify for alternative treatments to avoid the "free radical effect", whereas in the past they did not, thus improving their overall health.

However, it will take small but significant changes like this to inform providers to use *all* of their pre-medical knowledge, not just the medical aspect when diagnosing and treating patients. As for the importance of that *"knowledge"* so often stated in this communication-a non-medical friend of mine once said:

"The reason they (counselors and others) make you take classes like Biology, Chemistry, and Physics as a pre-medical candidate-is to 'weed out' potential ones who cannot understand complex concepts". I disagreed with him then as I do now. For by using those disciplines in conjunction with the practice of medicine, not only have the ill effects of the ***"Photosensitivity: Caution, 'Free Radical' risk".*** *contributing to illness been elucidated, but so have their treatments.*

Thank you for your time and consideration.

I look forward to hearing from you timely on this extremely important communication.

Respectfully, name withheld due to confidentiality. See attestation if warranted.

Bibliography:

- The LibreTexts libraries (Chemistry, Physics…) are Powered by NICE CXone Expert and are supported by the Department of Education Open Textbook Pilot Project, the UC Davis Office of the Provost, the UC Davis Library, the California State University Affordable Learning Solutions Program, and Merlot. We also acknowledge previous National Science Foundation support under grant numbers 1246120, 1525057, and 1413739. Legal. Accessibility Statement For more information contact us at info@libretexts.org.
- Introduction to Spectroscopy. Donald L. Pavia, Gary M. Lampman, George S. Kriz, James A. Vyvyan. Farmington Hills 27555 Executive Drive Farmington Hills, MI USA. 1305177827, 9781305177826. PP 784.
- Current Medical Diagnosis & Treatment 2022. Maxine A Papadakis, Stephen J. McPhee, Michael W. Rabow. Sixty-First Edition. A Lange medical book. McGraw Hill, New York and other locations. Copyright 2022. PP 1840.

C. Environmental Impact

(A) Claim for categorical exclusion under §§ 25.30, 25.31, 25.32, 25.33, or § 25.34 of this chapter or an environmental assessment under § 25.40 of this chapter.). **Claim for categorical exclusion by the petitione Robin L. Webb MD., MSc.**

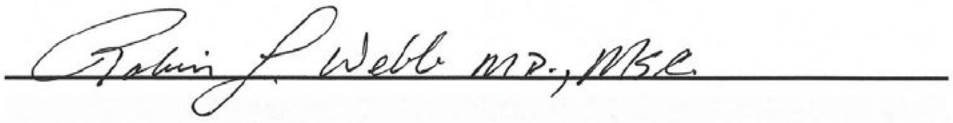
D. Economic Impact

(The following information is to be submitted only when requested by the Commissioner following review of the petition: A statement of the effect of requested action on: (1) Cost (and price) increases to industry, government, and consumers; (2) productivity of wage earners, businesses, or government; (3) competition; (4) supplies of important materials, products, or services; (5) employment; and (6) energy supply or demand. **Will await the Commissioner's review, Robin L. Webb MD., MSc.**

E. Certification:

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

(Signature):



(Name of petitioner): Robin L. Webb MD., MSc.

(b) (6)

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