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To the attention of Mrs Nathalie DUMARCET,

Head of the dermatology department,

Medicines medical directorate 2

of the ANSM National Security Agency of

medicine and health products

On January 07, 2023,

Madam, I take the liberty of writing to you following the joint committee convened by the ANSM on Tuesday March 2, 2021; Consisting of health professionals and patient representatives, concerning the monitoring and pharmacovigilance of isotretinoin, a committee responsible for examining and giving an opinion, in particular on the results of pharmacovigilance surveys carried out on pharmaceutical specialties based on isotretinoin (occurence of pregnancies exposed to isotretinoin and risk of occurrence of psychiatric disorders). »

I take the liberty of copying here the transcription of a passage from the committee's video published on March 10, 2021 on the ANSM's youtube channel : https://www.youtube.com/watch?v=iKS7E5fmExI , and therefore also from you copied here the transcription from 17 minutes and 22 seconds:

“ We have also received written contributions from patients which have been forwarded to us to the members of the committee and which will also be used to establish measures aimed at strengthening information on risks,

So, some, on the occasion of these written consultations, **there are points that have been addressed, to which we will respond more precisely in writing,** because as far as the mechanism of action of isotretinoin is concerned, it is a little complicated at the level of action on acne.

Well, that's a product that causes the dedifferentiation of keratinocytes, which means that it puts the sebaceous glands to rest. There may be, I suppose, that the questions were about: does isotretinoin act on other targets, elsewhere, in particular at the level of the brain perhaps, etc...

So that **requires a little more complicated answers because it's hypotheses that we... that are accumulated, so we could report on them, and share them with you...**

I ask you to remain focused on the objective of our session, which is to be a source of proposals on methods aimed at strengthening information, so that everyone is well informed, especially of the risks, because the effectiveness of the product, it is known all the same, it is an old product of more than 30 years, so today we are not going to reassess, neither the benefits nor the risks of this product, that was the subject other works, among others, there was a European arbitration which ended in 2018 and as Mrs Cristelle Ratinier said, to date, the balance between the benefits and the risks is still considered favorable... population, of course"

That said, I have been waiting for a year and 9 months for the written response that you promised. It was I who wrote the testimony 8 containing the questions to which you refer (which I am attaching to you at the end of this letter). You have my contact details in this letter. I await your answer.

And I'm certain that the thousands of people being collateral damage from your non-essential cosmetic medicine, to which some simple lifestyle rules can far outweigh its actual benefit/risk balance over a robust and expanded time window, at populational, therefore the **2300 people of the facebook collective** "Victims of Roaccutane (isotretinoin), Curacne, Procuta and generics", as well as **the people who posted 4835 comments** on the website of the Association of Victims of Roaccutane and Generics (AVRG), also await with impatience and curiosity your answers on these questions, all the questions asked.

Furthermore, I take advantage of this inevitable and annoying reminder, but clearly necessary, because I have other questions to ask you, as well as some remarks and suggestions, if you allow me:

How is it that I have no trace of the initial registration of the declaration of adverse effects and the understatement is weak, with your pharmacovigilance, initiated by my attending physician at the time, having had no no return from you…. yet being a textbook case, if one can say so, of collateral damage to your molecule.

I dare not imagine how many declarations are lost in a similar way.

These tedious, superficial considerations which should not take place being made , let's get to the bottom of the problem that concerns me (we?) :

- **1) first information on the risks, and therefore without even reassessing the risks (I will come back to this later), take into account not hypotheses, but established facts, which will therefore "accumulate" in this letter, to resume your wording.**

- **2) Secondly the reassessment of risks, this is fundamental research.**

1) risk information:

Isotretinoin has three levels of presence in the body:

a) short term: half-life of 46 to 48h (50% decrease in plasma level) b) medium term: approximately one month at the intracellular detection limit (except RNA) c) long term: up to one year to eliminate rRNA and put an end to the regulation of gene transcription.

Reference: https://www.ncbi.nlm.nih.gov/pubmed/9427083

Because of b) the "good" effects start to wear off and acne and sebum can potentially come back Because of c) (and therefore Isotretinoin's huge impact on HOX gene transcription), **why don't you recommend not having a pregnancy for a full year after stopping treatment?**

Because logically, as a precaution, the safest choice is to wait a year.

You advance an argument on the fact that this drug has been on the market for more than 30 years, to endorse your certainties about its mechanism, its "efficacy", and its benefit/risk balance.
The corollary of this argument could be: for
30 years, if the ANSM has been exempt from any conflict of interest, have you sufficiently questioned yourself?
Didn't you think that the research made discoveries, did you really take them into account?

Are you looking on the right side? What are you looking for?

Why do groups of people who have lost a loved one and more or less seriously disabled people exist in almost all Western countries for a drug being the first teratogen?

The second being depakine whose mutagenesis and transgenerational effect could be demonstrated.

Have you wondered how to explain the lag between intake and occurrence?
side effects?

On https://www.ehealthme.com/, one can find a Phase 4 clinical study, based on 30,990 people as of July 2019, who experience side effects from taking the Food and Drug Administration (FDA) drug Isotretinoin Accutane. The information analyzed by eHealthMe includes: side effects over time, by sex and by age.

It is obvious that during life, regardless of gender or age, it is the gastrointestinal disorders that persist and are at the forefront, the older the age, and the longer the time after taking increases:

Most common side effects over time (after stopping treatment):

<1 month:

• Pregnancy

• Suicidal ideation

• Reduced weight

• Inflammatory bowel disease

• Increased weight

• Anxiety

• Blurred vision

• Increased number of white blood cells

1 to 6 months:

• Rectal hemorrhage (bleeding from the anus) • Depression • Increased weight • Stress • Small bowel obstruction (blockage in the small intestine) • Dry lips • Anxiety • Xerosis (abnormal dryness of the skin or mucous membranes) • Gastrointestinal damage (damage to the gastrointestinal tract) • Vomiting **6 to 12 months:** • Inflammatory bowel disease • Suicidal ideation • Injury • Gastrointestinal damage (damage to the gastrointestinal tract) • Pregnancy

• Irritable bowel syndrome • Rectal bleeding (bleeding from the anus) • Ulcerative colitis (inflammation of the colon with ulcer) • Decreased weight • Depression **5 to 10 years:** • Inflammatory bowel disease • Bowel syndrome irritable • Injury • Rectal hemorrhage (bleeding from the anus) • Suicidal ideation • Depression • Gastrointestinal damage (damage to the gastrointestinal tract) • Decreased weight

• Ulcerative colitis (inflammation of the colon with ulcer) • Anxiety **10 years and over:** • Pregnancy • Inflammatory bowel disease • Increased weight • Anxiety

• Increased blood cholesterol • Crohn's disease (condition causing inflammation of the gastrointestinal tract) • Depression • Emotional distress • Stress • Suicide attempt **25 years:** • Injury • Ulcerative colitis (inflammation of the colon with ulcer) • Crohn's disease (condition causing inflammation of the gastrointestinal tract) • Depression • Intestinal obstruction • Suicidal ideation

• Unspecified rectal haemorrhage (bleeding from the anus) : • Suicidal ideation • Pregnancy • Decreased weight • Inflammatory bowel disease • Injury • Rectal haemorrhage (bleeding from the anus) • Suicide attempt

Most common side effects by gender:

Women :

• Suicidal ideation

• Inflammatory bowel disease

• Wound

• Reduced weight

• Irritable bowel syndrome • Pregnancy

• Increased weight •

Ulcerative colitis (inflammation of the colon with ulcer) • Depression

• Gastrointestinal damage (damage to the gastrointestinal tract)

Male :

• Inflammatory bowel disease

• Suicidal ideation

• Dry lips

• Suicide attempt

• Anxiety

• Small bowel obstruction (blockage in the small intestine)

• Vomiting

• Intestinal obstruction

• Stress

• Increased weight

Most common side effects by age:

0-1:

• Growth retardation (delayed growth) • Maternal drugs affecting the fetus (a chemical substance affecting the baby before birth taken by the mother) • Placenta previa (a condition that occurs during pregnancy when the placenta is abnormally placed and partially or completely covers the cervix) • Premature separation of the placenta • Baby small for dates (an unborn baby grows more slowly and is smaller than most babies of the same age) • Facial dysmorphism (an anatomical malformation of the face) • Feeling abnormal **2-9:** • Injury • Neuroblastoma (a cancer that forms in your nerve tissue) • Suicidal ideation • Arthropathy • Erythema (redness of the skin)

• Intestinal obstruction • Irritable bowel syndrome • Polyp • Reckless • Suicide attempt **10-19:** • Decreased weight • Suicidal ideation • Inflammatory bowel disease • Suicide attempt • Depression • Ulcerative colitis (inflammation of the colon with ulcer)

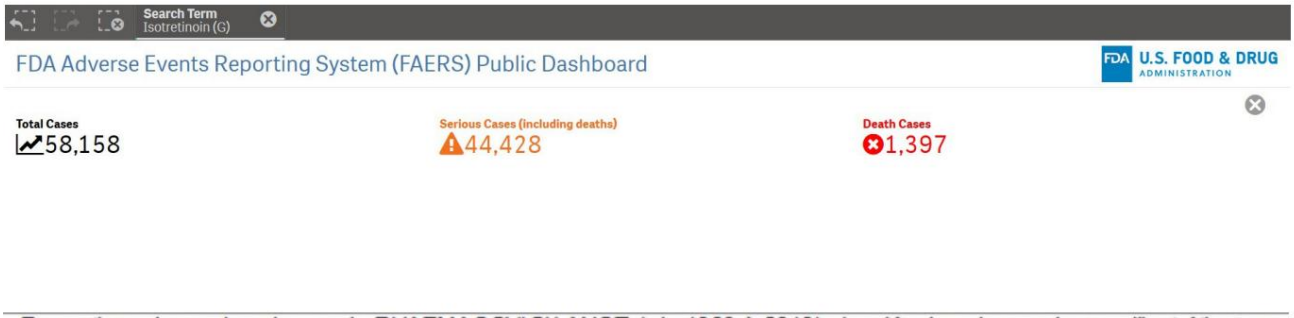
• Rectal hemorrhage (bleeding from the anus) • Dry lips
• Increased weight
• Irritable bowel syndrome
20-29: • Anemia (lack of blood)
• Alopecia (absence of hair in areas of the body) • Dry lips • Visual disturbance • Anxiety • Stress • Bowel obstruction • Abdominal pain
• Decreased weight • Suicidal ideation **30-39:** • Decreased weight

• Ulcerative colitis (inflammation of the colon with ulcer)
• Irritable bowel syndrome • Increased weight • Depression • Blurred vision • Suicide attempt • Rectal haemorrhage (bleeding from the anus) **40-49:** • Suicidal ideation • Syndrome of irritable bowel • Inflammatory bowel disease • Small bowel obstruction (blockage in the small intestine) • Decreased weight • Blurred vision
• Suicide attempt • Depression • Stress • Ulcerative colitis (colon inflammation with ulcer) **50 -59:** • Irritable bowel syndrome • Suicidal ideation • Injury • Stress • Inflammatory bowel disease • Rectal hemorrhage (bleeding from the anus) • Blurred vision • Dry lips • Increased weight • Ulcerative colitis (inflammation of the colon with ulcer) **60+:**

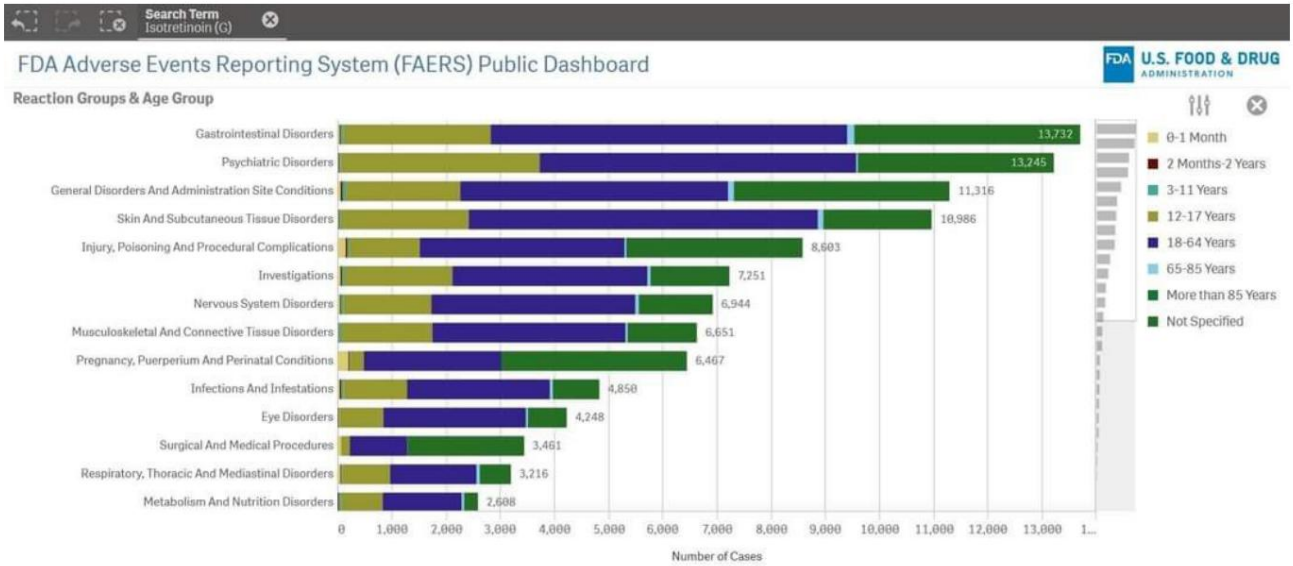
• Irritable bowel syndrome • Injury • Suicidal ideation

• Stress
• Small bowel obstruction (blockage in the small intestine) •
Dry lips

Moreover, according to WHO data in 2019, it is also gastrointestinal problems that are at the forefront, here too.



according to WHO , in pharmacovigilance reports, the first 4 major groups of iatrogenic diseases: 1) gastrointestinal problems (13%), 2) psychiatric disorders (12%), 3) dermatological disorders (11%), 4) "General disorders and administration site anomalies" (10%), d 'after vigiaccess.com.



Noting the very similar proportions of gastrointestinal problems, disorders

psychiatric disorders, and dermatological disorders, **have you sought to analyze the correlations and covariances?**

Have you tried to do principal component analyzes and factorial correspondence analyses, on your ANSM data, or on robust cohorts?

In order to understand what factors, what variables mean that some people, the majority of course, when we stay close to stopping the drug over time, will have nothing, and others will be disabled for life? In what proportions?

But also to detect all the false negatives, 25 years after taking or no correlation link is made, not to mention 5 years after taking?

Do you monitor the occurrence of gastrointestinal problems during the intake, and also during the life of a person disabled by taking this medication?

In the doctoral thesis of Mme LE MOIGNE defended on 20/10/2017: Illness autoimmune inflammation and acne: predisposing factors, clinical and therapeutic severity factors. Focus on Epidemiology of moderate to severe acne: Isotretinoin and psychiatric risk

This 2017 French pharmaco-epidemiological study, which is based on pharmacovigilance data and which concludes: "These results highlight that serious psychiatric events occurring during treatment with isotretinoin against acne are more likely to be related to isotretinoin itself than to the underlying disease (acne)." (page 71)

"All in all, in view of the data in the medical literature, the link between isotretinoin and psychiatric disorders is suspected but not proven. The published studies are numerous, of varied methodologies with discordant conclusions." (page 29)

"In conclusion, the health authorities apply the precautionary principle, by regulating the prescription/delivery of isotretinoin . **conducting studies to assess this risk or the populations most at risk." (page** 38)

"The medical literature is rich on the subject, with many references found on PubMed. However, in the end, few quality articles allow us to better understand this link. During our research, we found very many opinions of experts, commentaries, non-systematic reviews issuing varied opinions on the issue. **Despite the rich bibliography, few studies are of good methodological quality." (page** 39)

"Indication bias is confounding bias. It refers to the fact that a drug is given more in a patient with a high risk of complications." (page 58)

A new study to be completed in 2033 is based on the creation of the cohort COPAGNE. This DATA will make it possible to study the risk/predictive/prognostic factors of acne and isotretinoin.

“Several explorers in the Arctic or Antarctica have experienced hypervitaminosis A syndrome, after ingesting polar bear liver. This contains significant amounts of vitamin A (or retinoic acid or retinol). than polar bear liver and unfit for consumption.

reported https://claudegrandpeyvolcansetglaciers.com/2017/04/02/ “The consumption of polar bear meat can induce negative and even dangerous side effects. One of the most serious is hypervitaminosis A, an excess of the vitamin that can be contracted by eating the liver of polar bears, seals and walruses. Attacking the central nervous system, this condition can cause hair loss, flaking, fetal malformations, liver problems, vomiting, blurred vision and even death. Indigenous peoples have long been aware of this danger, as have explorers, although some did not feel sick after eating the liver of a polar animal. (page 28)

Why don't you sign a paper as detailed as the one included with the Zenatane of the USA on the risks of "depression" and "psychological disorders" in France?
In addition to the one on fetal malformations ?
Why even on the US signature paper, the impasse is made on chronic gastrointestinal problems? when they are actually on par with "psychiatric disorders" according to the WHO.

Here is a little Socratic dialogue from Dr. Bremner:
1. *Suicide is very common among adolescents, to whom Accutane is most often administered.*

Suicide is half as common among adolescents as among 20-somethings years.

Toddlers are the only age group with fewer suicides.

2. *Roaccutane is an acne medicine. How could he cause a*

depression?

Roaccutane is the brand name for isotretinoin, a compound that occurs naturally in the body and is a member of the retinoid family.
Retinoids bind to receptors in the brain and have neurological effects.
The skin and the brain come from the same developing place, the ectoderm. The fact that it acts on the brain provides a plausible biological mechanism by which it may cause depression.

Vitamin A is another retinoid known to cause psychosis, depression and other behavioral changes. The fact that a compound in the same class has similar effects is further evidence of a link of
causality.

3. *Scattered reports of depression do not prove that accutane causes depression. There is no epidemiological evidence that Roaccutane causes depression.*

Challenge-rechallenge studies, where patients are depressed when they take the drug, get better when they stop taking it, and get worse when they start it again, are considered the evidence of a causal relationship in the field of pharmacoepidemiology.

4. *There are no controlled clinical trials showing that* isotretinoin *causes depression.*

Controlled clinical trials are not required to show that a drug causes a particular side effect. For example, no studies have shown that high dose steroids can cause behavioral changes, yet this is a known side effect of these drugs. The drug manufacturer should conduct studies as part of post-drug monitoring. **In 2000, the FDA was discussing such a study with the manufacturer, but the study was never conducted.**

5. *I don't see depression with* isotretinoin *in my patients. You can develop depression with any medicine, cheerios or toothpaste. If it exists, it is sporadic or rare.*

Physicians should not base their decisions on their “clinical experience”. The literature supports an association based on established criteria that are used to assess the causality of drug side effects. A side effect may be seen in a minority of patients, but still exists and is causally related to the drug.

6. *The manufacturer claims to see no evidence of causation.*

So why do they list depression as a possible side effect of drug?

7. *Depression is very common. You can't say that the cases of depression on* isotretinoin *didn't happen by chance.*

About 16% of people develop depression at some point in their lives. However, only about 1% will develop it over a four month period. Isotretinoin studies show a rate of around 4-6%, which is higher.

8. *The 2005 Bremner study did not show that* isotretinoin *was the cause of the depression.*

The study was not designed for that. It was designed to examine the effects on brain function. Since only about 3% of people develop depression on isotretinoin, a study of 28 people would not be able to show it.

9. Isotretinoin *is an excellent medicine for acne. it would be a shame to*

withdraw from the market.

The fact that it works for acne does not relieve doctors of their responsibility to warn of the possibility of depression and monitor symptoms. People with a history of depression need to be monitored by a psychiatrist if they are taking isotretinoin.

pages 89/90 of https://www.govinfo.gov/content/pkg/CHRG-106hhrg73924/pdf/CHRG-106hhrg73924.pdf

Dr. Marilyn Pitts (FDA, Case Review) offered the following comments:

"The top 10 adverse events for Accutane include depression, ranked number 6. By contrast, we looked at tetracycline, which is another agent used for less severe acne. We have 8 cases of depression and 2 deaths, and we looked at Claritin in the AERS database where we have 10 cases of depression and 2 deaths.

In 1998, OPDRA analyzed spontaneous adverse drug event reports of positive dechallenge/rechallenge cases of depression, mania, psychosis, and suicide attempt. The 2998 case series supported the Accutane labeling change, which included a warning concerning psychiatric disorders. The warning stated that Accutane may cause depression, psychosis, and rarely, suicidal ideation, suicide attempts, and suicide.

In summary, we have 41 Accutane associated dechallenge/rechallenge cases. 76 percent were without a reported psychiatric history. The median time to onset of symptoms during the first course of Accutane was 30 days, and a median recovery time of 4.5 days. During the second course, or the rechallenge course, the time to onset of symptoms was shorter in the cases that provided the information. Also, after the second course of Accutane, depression persisted in some patients after discontinuation of Accutane and/or medical intervention. There was a possible dose-response to Accutane observed in 6 patients.

In conclusion, dechallenge/rechallenge cases provide strong evidence to support a link between a drug and an observed adverse event. We have presented 41 cases of positive dechallenge/rechallenge which provide further evidence to support a relationship between Accutane and depressive symptoms.

Dr. Wysowski (FDA, Postmarketing Experience Suicide and Depression), provided the following analysis:

"Over the 18-year period of marketing, the FDA received reports of 37 U.S. patients who committed suicide. 24 on Accutane and 13 after stopping the drug. Twenty two (22) percent of suicide cases were reported to have a psychiatric history. About 57 percent had other possible contributing factors for depression. n addition to the suicides, the FDA received reports of 110 U.S. Accutane users hospitalized for depression, suicidal ideation, and suicide attempt, 85 on Accutane and 25 after stopping the drug.

About a third of patients had positive dechallenges with psychiatric treatment, and nearly a third experienced persistent depression after drug discontinuation. one person had a positive rechallenge, while three others were rechallenged and were able to continue on Accutane with alcohol abstinence, dose lowering, and continued use of an antidepressant.

As of May 2000, the FDA received reports of 284 U.S. Accutane users with non-hospitalized depression. 45 percent were received in 1998 after depression and suicide were added as a warning to the labeling. About half of the non-hospitalized patients reported accompanying side effects such as dry mucous membranes, headaches, hair loss, and joint and muscle pain. About 50 percent of reports were from consumers and relatives, a higher proportion compared with most reports for most drugs.

The top 10 adverse events reported for Accutane include depression that ranks number 6. Of course, the degree of under-reporting is unknown and may be quite substantial.

There are several pieces of evidence supportive of a possible association between Accutane and depression and suicide. These include the relatively large number of reports of serious depression, more than for most drugs in the FDA's database, the temporal association between use of Accutane and onset of depression, positive dechallenges in individuals who felt better once Accutane was discontinued and psychiatric care was obtained, and positive rechallenges in individuals who experienced symptoms again after restarting the drug.

So, in summary, the FDA has received reports of suicide and serious depression in U.S. Accutane-treated patients. The case reports are suggestive of an association with Accutane, but do not allow definitive determination as to whether Accutane causes depression and suicide in treated patients."

Dr. Kathryn O'Connell (FDA, Biological Plausibility and Risk Management):

"The first item that I mentioned was we ask ourselves, do we see psychiatric adverse events? Have they

During the 2000 hearings on the safety of Accutane, the FDA mentioned 41 cases of depressed patients on isotretinoin, feeling better after stopping, then possibly taking the drug again, leading to a return of depression (HOR, 2001, p.
85).). This phenomenon is called "dechallenge/rechallenge" and goes a long way towards proving that the drug caused an adverse reaction.

Based on FDA data through 1998, it was reported that **76% of these patients had no experience of mental problems prior to isotretinoin; In addition, 33% remained depressed after stopping the drug (HOR, 2001, p. 85 - 86).**

Some may point out the small sample size, but again, it should be pointed out that the own drug regulatory agencies say that only 10-15% of significant side effects are disclosed by the

patients (HOR, 2001, p. 87).

More suicides occurred in patients taking isotretinoin than Prozac

between 1989 and 2003; the gap was 72 to 55 respectively (Sharav, 2004).

It seems that isotretinoin ended up on the list of 10 compounds

pharmaceuticals most linked to depression (Kontaxakis, Skourides, Ferentinos,

Havaki-Kontaxaki and Papadimitriou, 2009). Moreover, isotretinoin is the only

"non-psychotropic drug" from this list (Kontaxakis et al., 2009).

Let's do ONE more comparison between the drugs: Accutane and

the antibiotic minocycline. Both drugs are used to treat acne, although

minocycline is used to treat a number of different infections. Of the

UK data revealed number of prescriptions and side effects

treatment of the two drugs between the beginning of the 1970s and 1997. 50,000 patients

were treated with Accutane and 6.5 million were treated with minocycline (HOR,

2001, p. 83). . It is therefore natural that you would expect minocycline to be

associated with a greater number of mental side effects, because it was administered

to a greater number of patients and that there was a much higher risk of

problems. Due to the large disparity between the number of prescriptions, the number

of mental adverse effects must be converted into a percentage before they want

say nothing to anyone. **Minocycline was prescribed 1300 times more than Accutane.**

So what was the number of **mental side effects reported** during these

years for both drugs? **Minocycline: 45 Accutane: 135** (HOR, 2001, p. 83).

Why, after each wave of trials, in the USA, then in Europe, the princeps

is withdrawn from the market but the generics continue?

And if, in 2010, a patient who took accutane in the USA, having triggered a Chron's disease, and having had to undergo a removal of part of the intestines, then would have attacked the Roche laboratory, to then be “compensated”, not to say “bought for his silence”, to the tune of 25 million dollars, because the cabinet lawyers in the usa: https://www.seegerweiss.com/ would have indicated that there were hidden mammal studies, conducted by Roche, which revealed that could Accutane damage the intestinal mucosa?

This is obviously only an “accumulated” hypothesis among other facts and hypotheses...

And if all this debate and questions about whether or not , isotretinoin triggers "clinical depressions" or not, only served to focus attention on the tree that hides the forest, to hide the root of the problem, and therefore not to speak, that roaccutane destroys the intestines in the first place irreparably, the “depressions” observed at the clinic, the anamnesis, the nosology, and the diagnosis purely pseudo-scientific differential, being only syndromes of organic, second-order exhaustion, mixed with a non-recognition and a no explanation of the first-order causes and consequences of this molecule?

What could be called reductionist and scientist in this state of affairs?

Now let's talk about solutions for better informed consent, you won't be able to not say that you did not know how to do it, unlike us, who had the impression of having been scammed:

– **2) reassessment of risks, this involves basic research.**

Introduction for the beginner: genetic databases

When studying the (side) effects of isotretinoin, there are many

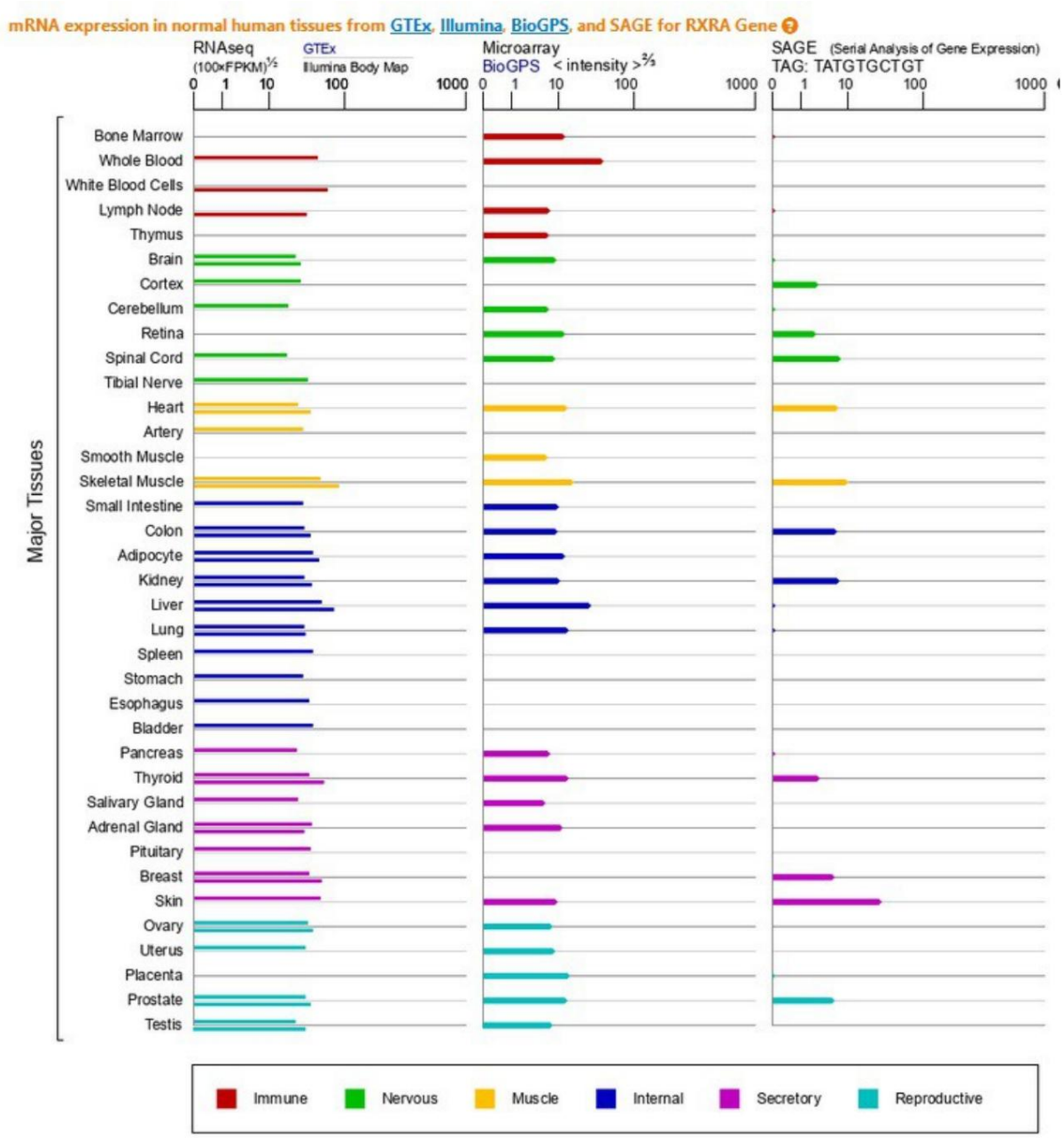
similarities between apparently very different effects. One of the reasons for this is gene expression. A gene that is expressed in the skin can also be widely expressed in cells of the brain, liver, kidney, heart and many other cells. This is the case of the retinoid X receptor, RXR, which is strongly affected by the retinoid 13-cis-retinoic acid (Roaccutane). This means that when the substance is used in very high doses, all cells that carry these receptors will be affected. As an example, let's look at this retinoid receptor by looking at a gene database.

Genecards - RXRA (Retinoid X Receptor Alpha)

https://www.genecards.org/cgi-bin/carddisp.pl?gene=RXRA

RXR comes in three forms. We will take a look at RXRalpha (RXRA).

And again, as if by chance, we see that his expression is not confined to sebaceous glands... On the contrary...



It is expressed everywhere: Hormonal, reproductive, intestinal, immune system, musculoskeletal, nervous...

Anything to add on these “accumulated assumptions”?

Is it necessary for you to interpret these factually factual facts? Don't you have any not aware? That would surprise me a lot.

This gene is overexpressed in whole blood, liver, intestine, system immune system, gallbladder, placenta, reproductive glands...

Where is the gene expressed ?

The genetic map for RXRA contains a box where the expression of the receptor is listed in different parts of the body. (Said "tissue" "clones by gene" "clones totals"). A high expression means that there are many copies of the receptor.

Related genes

This is a very useful section, because if a gene is linked in its structure (has a sequence that recalls the gene sought), in this case RXRA, we find that these genes are also very likely to be affected. In the case of RXRA, since we know that it is affected, we may discover that other receptors within these families with high certainty are also affected. In this case, it turns out that RXRA has many related genes and also affects many genes secondarily:

InterPro Domains and Families:

IPR008946 Str_ncl_receptor

IPR000003 RtnoidX_receptor

IPR001628 Znf_C4steroid

IPR001723 Stdhrmn_receptor

IPR000536 Hrmon_recept_lig

Sequences

Generally the sequences (of the "small amino acids" - nucleic acids, of which is constituted the gene) do not say much, **if they are not analyzed with powerful computer tools (what are you waiting for the fare?).** However, some short sequences can tell a bit more about the linkage of the residues and the

transcription.

Cut

Different genes have different sizes.

Other information

The genetic map contains much more useful information, such as references to studies done on the gene, similarities between different species and more Again. Genetic maps are powerful tools for biochemical research and many databases are publicly available.

Future use of substances that significantly affect expression multilevel genes

Substances used for cancer such as isotretinoin affect the expression of genes at multiple levels. Today there are good methods such as RT-PCR and Western blot, to determine factors such as: which genes are affected, what binding affinity to the substance they have and what role they play in the cell.

There is less use of large and well-functioning determination rates of the site-directed mutagenesis/deletion of transcriptional promoter sites (by mutagenesis occasional) in association with exposure to substances very likely to cause mutagenesis, although studies involving the induction of point mutagenesis to exist.

New broad and accepted methods needed to determine and report the statistical rate of mutagenesis

A general problem is determining and reporting the prevalence of mutagenesis punctual. Some methods are discussed in Bajaj et al (2005) **[1].** Declare the rate point mutagenesis statistic is of utmost importance, not only in the case of Roaccutane and other cancer treatments, but for all substances that significantly influence gene expression. The rate of one-time mutagenesis will undoubtedly have an impact on **the long-term health of patients.** Factors such as downregulation of the function of certain types of receptors due to deletions of promoter binding sites can affect many significantly the reappearance of cancer, the development of diabetes, cardiovascular disease and other diseases.

I am convinced that the future of medicine therefore depends on:

1) A broad statistical method for determining the overall probability of significant point mutagenesis of various critically important genes, regardless of regardless of the substance used and the dose.

2) In the case of significant point mutagenesis that might be expected in several areas, for example with toxic exposure, inhibition significant receptor or growth factor inhibition, *broad and accepted statistical method* for the determination and reporting of rate in percentage and in ranges of mutagenesis given determined for the subjects critically important *genes , dose* of the substance used and *time* of use. These reported data may, in clinical practice, be used additional information very adequate in the decision of the correctness of the clinical use of any substance.

Simplified example of declaration of mutagenesis

An example statement might look like this:

x Name of substance: Cancer substance X

x Clinically relevant rate of mutagenesis/deletion of promoter sites

transcriptional: Yes

x Determination of critical areas for point mutagenesis

x Receptor Subtypes Affected: Q Receptor Family

x Targeted transcription factors: Sp1, Sp3

x Estimated reduction in residue/protein function with removal of sites

transcriptional promoters: 80%

x Active/inactive phenotype: Active with low and high initial expression

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x Dose/plasma concentration 0.1A

Mean Site Mutagenesis Rate for Receptor/Receptor Family Q

with time 1, 2 and 3

Deletion of functional Q receptor transcriptional promoter sites with the

time 1: interval: 3% to 5%

time 2: 8-12%

time 3: 12-16%

x Dose/plasma concentration 0.5A

Mean Site Mutagenesis Rate for Q Receptor/Receptor Family

with time 1, 2 and 3

Deletion of functional Q receptor transcriptional promoter sites

with

time 1: range: 15% to 25%

time 2: 30-40%

time 3: 40-55%

x dose/plasma concentration 1.0A

Mean Site Mutagenesis Rate for Q Receptor/Receptor Family

with times 1, 2 and 3

Deletion of functional sites of the Q receptor transcriptional promoter

with the

time 1: range: 45% to 60%

time 2: 70% to 85%

time 3: > 95%

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x Conclusions, discussion of results and prevalence of cancer recurrence

according to the statistical rate of the negative regulation of the function of the

receptors due to mutagenesis.

References:

[1] Bajaj, K., Chakrabarti, P., and Varadarajan, R. *Mutagenesis-based definitions and probes of residue burial in proteins* (2005) Proc. Natl. Acad. Science. USA, 10.1073/pnas.0505089102

Thank you for keeping your promise of March 21, 2021, in my person as well as the

2300 people from the facebook collective “Victims of Roaccutane (isotretinoin), Curacne, Procuta and generics”, as well as **the people who posted 4835 comments** on the website of the Association of Victims of Roaccutane and Generics (AVRG), and of answer in detail on what you intend to improve or not concerning this long-term scourge of isotretinoin . Would give it to your future children, knowing all of this?

Best regards,

firstname name

ANNEX

Testimony 8 ANSM committee March 2021

https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&cad=rja&uact=8&ved=2ahUKEwiUyZSbgbb8AhWJXqQEHbQzBBUQFnoECAkQAQ&url=https://archiveansm.integra.fr/content/download/192783/2522707/version/1/file/20210310_Temoignages_Collective_Facebook_Victimes_Roaccutane.pdf&usg=AOvVaw0aRtmTmFzwDSPVzJiuKV6A

" Hello,

I took one of the generic Roaccutane (isotretinoin) 16 years ago at the age of 19 years. Having at that time a completely correct, balanced life, being in excellent health both physical and mental, without any history, athletic, pursuing studies academics, my life then changed in the years that followed.

To know that for my acne, the dermatologist offered me Roaccutane after a few trials of various creams, without first going through antibiotics. There exists, in no more ignorance and preconceived ideas maintained even by dermatologists, of the effects of this molecule, a very great laxity concerning its prescription.

Result for me: recognized as more than 50% disabled. My life is way below my potential. My case is far from isolated, even if you are not yet aware of it.

Alopecia, excessive sweating, chronic ORGANIC exhaustion (“depression”), digestive problems, cognitive problems, joint pain...etc.

Most chronic post isotretinoin sufferers present the same picture clinic of intersecting autoimm̄une syndromes (fibromyalgia, polyarthritis rheumatoid, chronic fatigue syndrome, Gougerot Sjögren's dry syndrome) p̄ast in silence, a painting that officially does not exist, despite the number of victims...

I then discovered with amazement after several years, that isotretinoin is metabolized by isomerization to tretinoin, an anti-cancer molecule used in leukemia acute (and previously for glioblastoma cancers). The effects are almost same but with different intensities and frequencies, according to the two notices of the two drugs. **[1][2][3].** However, these effects appear to be largely underestimated - for isotretinoin.

During an anti-acne treatment (between 40 and 80 mg of isotretinoin for a man

of 80 kg), it is metabolized at most by isomerization ¼ (between 10 and 20 mg of tretinoin) of the average usual dose (80 mg of tretinoin) of chemotherapy anti-cancer (Vesanoid is prescribed in acute pro myelocytic leukemia (LAP)) [1][4].

We may wonder how to explain that the side effects would be 100 times to 1000 times less important according to the notices of the two drugs with only 4 times less Tretinoin metabolized?

And this contradicts the very numerous testimonies.

This analogy between Isotretinoin Tretinoin deserves to be fully verified. In Indeed, no one would want to maintain a drug that causes a form of premature and insidious aging to millions of adolescents and young adults suffering from acne. If cells have shorter telomeres and downregulation of the enzyme telomerase **[7],** they approach the Hayflick limit and cannot divide and proliferate as much as before being damaged. They then undergo a growth arrest senescence and/or cell death (apoptosis).

It is this mechanism which acts against acne, by destroying the sebaceous glands, and which causes accelerated renewal of the skin, to the detriment of aging accelerated. This means enormous significant implications in order to maintain a adequate cell proliferation throughout the body for the rest of an elder's life patient. Major groups of affected organs in pharmacovigilance statistics are precisely those whose cells reach their limit of Hayflick because they have the shortest renewal time. This would explain also the time lag often reported between taking and the onset of effects disabling secondary (time to reach Hayflick limit).

It is imperative to understand that stopping Isotretinoin does not necessarily mean

that its effect wears off. There are a large number of reports of people who claim that some of their side effects, especially the worst types, are not only appeared years after stopping isotretinoin. According to FDA data, inflammatory bowel disease and "depression" still present 20 years after the treatment (with progressively a first place for the disorders various intestinal disorders, supplanting depressions and suicides). **[6]**

Contrary to what the leaflet claims, this medicine therefore appears to have an effect chronically latent on people's bodies. This also raises the question of the aspect transgenerational if the germ cells are affected, and everything suggests that yes (number 1 teratogen, number 2 being Depakine whose mutagenesis has been demonstrated).

Larger scale pre- and post-treatment studies should be conducted by performing CT scans of the hippocampus and the subventricular area of the brain **[5].** A test in telomere length before and after treatment in a robust patient cohort would also be very sensible.

A specific study of tissue biopsies of different organs and blood tests before and after treatment with Isotretonin could identify the extent to which cell division was reduced.

In addition to these necessary studies, the notice is erroneous: it does not declare any mutagenesis and states that side effects suggestive of hypervitaminosis A have been spontaneously reversible after interruption of isotretinoin, it must be reviewed in order to be able to talk about informed consent.

A care pathway should be created with joint monitoring between the dermatologist and the general practitioner, focusing on the occurrence of gastrointestinal disorders first place, more tangible and less questionable than "depression" as well as a care and

smart recovery focused on gut microbiota.

Thanks for reading me. »

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[1] instructions for anti-acne PROCUTA 20 mg, soft capsule (isotretinoin)

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specid=67952249&typedoc=R&ref=R0194594.html

5.2 Pharmacokinetic properties, Metabolism

[2] Vesanoid (Tretinoin) anti-cancer leaflet

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[3] instructions for Roaccutane by Roche (Isotretinoin)

https://www.roche.be/fr/produits services/nos medicaments/roaccutane isotretinoin.html

https://www.eÿnotice.be/fr/notices/scientifique/2063/1261

[4] leaflet of Vesanoid, 10 mg, soft capsule (Tretinoin)

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[5] James Crandall, Yasuo Sakai, Jinghua Zhang, Omanand Koul, Yann Mineur, Wim E. Crusio, and Peter

McCaffery. 13 cis retinoic acid suppresses hippocampal

cell division and hippocampal dependent learning in mice PNAS April 6, 2004

https://www.pnas.org/content/101/14/5111.full

[6] Accutane side effects by duration, gender and age in a phase IV clinical study

https://www.ehealthme.com/drug/accutane/sideÿeffects/

[7] Frédéric Pendino, Maria Flexor, François Delhommeau, Dorothée Buet, Michel Lanotte, and Evelyne

Segal Bendirdjian*, Retinoids down regulate

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