

Risk of sensitization to preservatives estimated on the basis of patch test data and exposure, according to a sample of 3541 leave-on products

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Summary

Background. The risk of sensitization cannot be derived from the frequency of sensitization to allergens alone, but exposure should be considered.

Objective. To estimate the risk of sensitization to selected preservatives.

Methods. The occurrence of preservatives in 3541 leave-on products based on the labelling of the ingredients was documented. Frequency of sensitization to preservatives was analysed on the basis of Information Network of Departments of Dermatology data for 2006–2009. As an estimate of sensitization risk, the sensitization exposure quotient (SEQ) was calculated as the quotient of the relative frequency of sensitization and the relative frequency of use.

Results. The SEQs varied greatly, offering a ranking regarding risk of sensitization: phenoxyethanol (SEQ: 0.06), benzyl alcohol (0.30), parabens (0.35), sorbates (0.92), benzoates (1.35), formaldehyde-releasers (1.6), methylisothiazolinone (MI) (1.7), iodopropynyl butylcarbamate (3.4), methylchloroisothiazolinone/MI (9.0), and 2-bromo-2-nitropropane-1,3-diol (13). There was a good correlation between the ranking of substances according to potency (hazard) and the ranking of the SEQ (risk).

Conclusion. High frequencies of sensitization may be put into perspective by the frequent use of certain preservatives. Despite infrequent use, others (with higher potencies or too high use concentrations) may turn out to be associated with an increased risk. Hazard assessment should be supplemented by risk assessment.

Key words: allergic contact dermatitis; cosmetics; exposure; leave-on products; preservatives; risk; sensitizer.

The frequency of sensitization to allergens observed in large samples of patch-tested patients reflects their impact as contact allergens in absolute terms. On the basis of the absolute frequency of contact sensitization observed, or on extrapolations to the population level (1), the

question can be answered as to whether these figures are a reason for concern, indicating a threat to the health of the population, or otherwise. However, the question of whether substance A poses a lower allergenic risk than substance B, which should therefore be replaced in products by substance A, cannot be answered. Such risk assessment must also take into account exposure data, that is, relate the absolute risk to the frequency of exposure, thus arriving at a 'relative incidence' (RI) (2) or, more generally, at a 'relative risk'.

In a former study, it was possible to relate extrapolated annual frequencies of sensitization (incidence) to

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topical drugs in the general population (3) to the amount of drugs sold [defined daily doses (DDDs) per year], and calculate an RI (2). For example, sensitization to gentamicin was more prevalent than sensitization to kanamycin (2077 vs. 1366 cases with periorbital dermatitis caused by the ingredient, per year, at the population level), but prescription via ophthalmological drugs in terms of DDDs was about three times higher for gentamicin than for kanamycin (43.3 vs. 15.4 mil DDD per annum). Thus, the ranking of sensitization risk was actually reversed: the RI (cases/100 000 DDD-year) for gentamicin was 4.8, and that for kanamycin was 8.7. Thus, exposure to kanamycin turned out to be associated with a greater risk of sensitization (2).

Preservatives are generally used in cosmetics, household products and in industrial applications. Although the amount used in industrial products might be known [e.g. for formaldehyde, 26 153 tons per year are used, and formaldehyde is contained in 2363 products (4) in Denmark], the amount coming into contact with the skin is unknown. Therefore, these data cannot be used as 'skin exposure data'. The situation is different regarding cosmetics, in particular leave-on cosmetics. These are (i) explicitly meant to be used on the skin and (ii) provide full qualitative labelling, except for most fragrances, but including preservatives. Therefore, we set out to relate frequencies of sensitization to the exposure to preservatives via leave-on cosmetics, quantified by the number of products containing the preservative in question.

Methods

Exposure to preservatives contained in cosmetics

Labelling of cosmetic products ($n = 5451$) was documented by the Chemisches und Veterinäruntersuchungssamt Karlsruhe/Germany (CVUA), with the products being aggregated into 24 classes. Products were purchased between 2006 and 2009 at random for official investigation in terms of conformity with legal provisions.

Only leave-on products ($n = 3541$) were considered. Within this group of products, 6401 occurrences of preservatives were documented following the obligatory INCI-declaration of the ingredients (INCI: International Nomenclature of Cosmetics Ingredients). Thus, a leave-on product contained 1.8 preservatives on average. As the frequency of occurrence of a preservative in those leave-on products indicates, in some respects, actual exposure, real exposure in terms of quantity could not be considered, because the concentration of the preservatives in the products was unknown. Therefore, the frequency of occurrence is used as the basis for further analysis.

A number of adjustments to the 'crude' use figures were employed before relating frequency of use to patch test results:

- Only those preservatives were considered that were patch tested by the Information Network of Departments of Dermatology (IVDK) (see below).
- Preservatives that were patch tested but not, or very rarely ($<0.5\%$), found in products included in the sample of leave-on cosmetics, namely, formaldehyde, quaternium-15, chloroacetamide, DMDM hydantoin, and methyldibromo glutaronitrile, were not considered in this analysis.
- As sodium benzoate (but not benzoic acid) and sorbic acid (but not potassium sorbate) were patch tested, the frequencies of use of the acids and salts were added up to give 'benzoates' and 'sorbates' (Table 2).
- Parabens were patch tested as a mix containing methylparaben, ethylparaben, propylparaben, and butylparaben. However, in products, single parabens were separately declared. Altogether, there were 4128 occurrences in the leave-on products, documented by the CVUA, namely, of one paraben in 13.4% of products containing any paraben, of two in 34.7%, of three in 9.9%, and of four in 42.1%. To arrive at an estimate of the proportion of products containing parabens, the use of the four single parabens was added up and divided by 2.8 (the weighted average of the number of parabens according to the above data). Thus, the number of 'paraben occurrences' (corrected for their multiple use) was 1474, and the number of paraben occurrences not considered was $(4128 - 1474) = 2654$. The final number of preservative occurrences considered was $(6401 - 2654) = 3747$. This figure served as the reference for calculating the relative share of preservatives.
- As the formaldehyde-releasers imidazolidinyl urea and diazolidinyl urea (5, 6), as well as the isothiazolinones methylchloroisothiazolinone (MCI)/methylisothiazolinone (MI) and methylisothiazolinone (MI) by itself, very often cross-react (7, 8), the use of imidazolidinyl urea and diazolidinyl urea was added up to give exposure to 'formaldehyde-releaser', and the use of MCI/MI and MI was added up to give exposure to 'isothiazolinones' (Table 2), as formaldehyde-releasers and MCI/MI vs. MI alone, respectively, are very rarely combined in one product.

On the basis of the total frequency of use of the preservatives considered ($n = 3747$), the relative frequency

Table 1. Modified MOAHLFA index of patients positive for at least one of the preservatives considered to be positive as compared with patients negative for each of these, and the profile of patients positive for each single allergen

	No.	Male M	Atopic dermatitis A	Hand dermatitis H	Face dermatitis F	Age 40+ years A
Positive for at least one preservative	1201	36.5	24.5	26.6	21.6	76.8
Negative for all preservatives	17 024	34.2	21.8	24.5	22.8	69.5
Positive for:						
MCI/MI	373	30.6	22.3	24.4	22.0	78.6
2-Bromo-2-nitropropane-1,3-diol	245	40.0	25.7	27.8	17.6	84.5
Diazolidinyl urea	108	27.8	29.6	14.8	39.8	63.9
Sodium benzoate	137	51.1	37.2	19.7	18.3	55.5
Imidazolidinyl urea	106	28.3	34.0	19.8	35.9	60.4
Sorbic acid	98	48.0	20.4	44.9	6.1	82.7
Benzyl alcohol	31	16.1	22.6	38.7	12.9	67.7
Methylisothiazolinone	88	36.4	17.1	27.3	23.9	77.3
Iodopropynyl butylcarbamate	126	37.3	28.6	30.2	12.7	73.8
Parabens	211	54.0	26.1	27.5	18.5	77.3

MCI, methylchloroisothiazolinone; MI, methylisothiazolinone.

Phenoxyethanol excluded (only three positive reactions).

of use of preservatives was calculated as the share of products (%) containing the respective preservative (Table 2, column 6).

Frequency of sensitization

Data for patients tested with the standard series and the preservative series between 2006 and 2009 in the departments of the IVDK were analysed with a focus on the frequency of sensitization to preservatives contained in these series. Patients with suspected occupational dermatitis or leg dermatitis were excluded from analysis, as in both cases important non-cosmetic risk factors would interfere. Thus, the population considered can be regarded as exposed to cosmetics *in sensu strictu*. To characterize the study population, the remaining factors (M, A, H, F, A) of the MOAHLFA index were analysed [MOAHLFA: the proportion of men (M), and of patients with occupational dermatitis (O), with atopic dermatitis (A), with hand dermatitis (H), with leg dermatitis (L), with face dermatitis (F), and being at least 40 years old (A)], comparing those with at least one positive reaction to a preservative with those showing no reactions to preservatives (Table 1). In Table 2, the frequency of sensitization to MI is given (i) as is and (ii) corrected for the proportion of MI-positives not reacting concomitantly to MCI/MI (33%) (9). Frequencies of sensitization to single preservatives were added up to give the total frequency of sensitization to preservatives. The relative frequency of sensitization was calculated as the share of sensitization to a single allergen (%) relative to the total of sensitization to preservatives (Table 2, column 4).

Sensitization exposure quotient (SEQ)

As an estimate of sensitization risk associated with exposure to the respective preservative, the SEQ is calculated as the quotient of the relative frequency of sensitization divided by the relative frequency of use (Table 2, column 7).

Results

The MOAHLFA index (modified, as patients with occupational or leg dermatitis were excluded by design) of patients positive for at least one of the preservatives considered in comparison with patients negative for each of these, and the profile of patients positive for each single allergen, are presented in Table 1. The overall profile of positives did not differ from that of negatives. The profile of imidazolidinyl urea and diazolidinyl urea was remarkable in terms of frequent face dermatitis and less frequent hand dermatitis, compatible with the assumed cosmetic exposure. The reverse pattern was found for iodopropynyl butylcarbamate and 2-bromo-2-nitropropane-1,3-diol, which could be associated with unidentified occupational exposure. The profile of MCI/MI and MI was interpreted as undetermined with regard to the source of exposure. In a recent analysis, sensitization was (very) often associated with occupational dermatitis (9), which, again, may be remained undetected in our dataset. The remainder of the allergens are frequently used in cosmetics, but their profile is inconspicuous in this regard, except for a very high proportion of males among those testing positive with parabens, sorbic acid, and sodium benzoate (compatible with an increased susceptibility of the male

Table 2. Sensitization exposure quotient (SEQ) (values in column 7 in bold), derived from the allergy share of single preservatives (where the total of allergies to preservatives is 100%) divided by the product share (the relative occurrence of preservatives in products)

Preservative allergens in leave-on products	2 n (tested)	3 % positive	4 Allergy share (%)	5 Products (n)	6 Product share (%)	7 SEQ
Phenoxyethanol ^a	4995	0.14	1.64	1111	29.6	0.06
Benzyl alcohol	17 740	0.17	1.99	245	6.5	0.30
Parabens	17 925	1.18	13.79	1474	39.3	0.35
Sorbates (acid/potassium)	17 855	0.55	6.43	261	7.0	0.92
Benzoates (sodium/acid)	17 740	0.77	9.00	250	6.7	1.4
Imidazolidinyl urea	17 880	0.59	6.89	102	2.7	1.6
Diazolidinyl urea	17 872	0.60	7.01	65	1.7	1.6
Methylisothiazolinone ^b (MI)	6570	0.40	4.67	28	0.7	1.7
Iodopropynyl butylcarbamate	17 857	0.71	8.29	92	2.5	3.4
Methylisothiazolinone ^c (MI)	6570	1.34	14.11	28	0.7	5.1
Methylchloroisothiazolinone/methylisothiazolinone (MCI/MI)	17 918	2.08	24.3	73	2.0	9.0
2-Bromo-2-nitropropane-1,3-diol	17 935	1.37	16.0	46	1.2	13
Formaldehyde-releaser	—	—	—	167	4.5	—
Isothiazolinones	—	—	—	101	2.7	—

^aPhenoxyethanol was not patch tested between 2006 and 2009. Data are taken from a former period.

^bOnly those considered not reacting concomitantly to MCI/MI (33%) (9).

^cMI not corrected for concomitant reactions to MCI/MI.

sex to irritant compounds; this is not further discussed here) (9)).

The results are presented in Table 2. The frequency of sensitization ranged from 0.14 (phenoxyethanol) to 2.08 (MCI/MI) (Table 2, column 3). The relative frequency of sensitization ranged from 1.64% (phenoxyethanol) to 24.3% (MCI/MI) (Table 2, column 4). Of the products, 39.3% contained parabens, and 0.7% contained MI (Table 2, column 6). The total of formaldehyde-releasers reached only 4.5% (imidazolidinyl urea, 2.7%; diazolidinylurea, 1.8%). More rarely used were the isothiazolinones (2.7%; MCI/MI 2.0% and MI 0.7%), iodopropynyl butylcarbamate (2.5%), and 2-bromo-2-nitropropane-1,3-diol (1.2%).

The ranking of SEQs (Table 2) differed greatly, each indicating a different risk of sensitization relative to the preservatives considered: phenoxyethanol (SEQ: 0.06), benzyl alcohol (0.30), parabens (0.35), sorbates (0.92), benzoates (1.4), formaldehyde-releasers (1.6), MI (1.7), iodopropynyl butylcarbamate (3.4), MCI/MI (9.0), and 2-bromo-2-nitropropane-1,3-diol (13).

From these figures, it can be concluded that, if one is exposed to, for example, MCI/MI or iodopropynyl butylcarbamate, the risk of becoming sensitized is apparently higher than with exposure to parabens or benzyl alcohol.

Discussion

Up to now, the importance of preservatives as contact allergens has been expressed only as the absolute

frequencies of sensitization found in patch test populations (9–11). There is a group of substances (group I) with sensitization frequencies above 1%, including MCI/MI, methyldibromo glutaronitrile, formaldehyde, 2-bromo-2-nitropropane-1,3-diol, parabens, and MI (9). In a second group (group II), sensitization frequencies are below 1%: this comprises iodopropynyl butylcarbamate, formaldehyde-releasers, benzoates, sorbates, benzyl alcohol, and phenoxyethanol. The substances of group I could be regarded as important allergens, and those of group II as less important or even unimportant. These different frequencies of sensitization could simply reflect the frequencies of use: those of group I would then be frequently used, and those of group II more rarely. We wondered whether this explanation holds true when referring to the actual use of preservatives. A perfunctory look at the statistics of use already shows that this is not always the case. MCI/MI, for example, is the most important allergen in terms of allergy frequency, but is rarely used in leave-on cosmetics. Phenoxyethanol, at the lower end of the allergy statistics, is widely used. One may conclude that the risk of becoming sensitized to MCI/MI must be higher than that of becoming sensitized to phenoxyethanol. For other substances, there may be some correlation between sensitization and use, for example in the case of parabens (frequent sensitization/ frequent use) or benzyl alcohol (infrequent sensitization/limited use). However, no direct conclusions (as above) regarding the risk of sensitization are possible in these cases. For comparison of the different allergy–use relationships, we calculated an SEQ, taking into account the relative use of substances considered

for analysis and the relative frequency of sensitization. As mentioned above, exposure to single preservatives in terms of quantity was not included in this analysis, as the use concentrations were not known. Rather, the SEQ can be regarded as an estimate of sensitization risk associated with qualitative exposure to the respective preservative. The degree of risk attributed here to a chemical is based on the ranking of SEQs, which is (only) relative within the set of preservatives considered. It can thus not be conceived as 'relative risk' in a strict sense, that is, relating (sensitization) risk to a certain reference in measurable units.

The risk of becoming sensitized is obviously negligible in the case of phenoxyethanol, and very low in the case of benzyl alcohol and the parabens. The 'importance' of the parabens as sensitizers (>1% sensitized) is clearly put into perspective by the low SEQ. A moderate risk can be attributed to the benzoates, sorbates, formaldehyde-releasers, and MI. Benzoates and sorbates, on the one hand, and the two formaldehyde-releasers imidazolidinyl urea and diazolidinyl urea, on the other hand, did not differ with regard to the sensitization risk according to our analysis. Formaldehyde is not used in cosmetics, but the amount released may be high enough to elicit allergic contact dermatitis (5, 12). The risk of sensitization to MI could be regarded as moderate, although it was considered to be safe for use in leave-on cosmetics (13). Further continuous surveillance and analysis is needed in order to identify problematic products (e.g. moist toilet paper) and subgroups at risk, such as patients with peri-anal eczema (14, 15). It is not clear to what extent primary exposure and sensitization to MCI/MI contributed to positive concomitant (cross-)reactions to MI. In restricting the analysis to those who reacted only to MI, but not to MCI/MI, we tried to account for this scenario. Primary sensitization to MI has been observed (16–18).

The risk of sensitization to iodopropynyl butylcarbamate is not negligible. The quantitative risk assessment (QRA) approach has been critically commented on and has still to prove its validity (19); this is illustrated by the observation that the 'typical exposure' to cosmetics has been found not to exceed the 'acceptable exposure', except only for the maximum permitted level in non-aerosol deodorants (20), which seems to be in some disagreement with the risk assessment presented. This example shows that the QRA approach should be subject to continuous external validation, and possibly refinements (19).

An unequivocally high risk of sensitization is associated with exposure to MCI/MI and 2-bromo-2-nitropropane-1,3-diol. Although MCI/MI is permitted as a preservative for all cosmetics, including leave-on products, only the use in rinse-off products was regarded as safe by the European Commission's risk assessors (21). Nevertheless, 2% of

leave-on products contained MCI/MI, despite the fact that MCI is the most potent allergen among the preservatives.

Although 2-bromo-2-nitropropane-1,3-diol has been known as an allergen for a long time (22, 23), the high risk associated with exposure to it has not yet been appreciated. The potency of 2-bromo-2-nitropropane-1,3-diol may be in the range of that of iodopropynyl butylcarbamate or even higher, but twice of that of MI. It has at least 1/100 of the potency of MCI (Table 3). However, the SEQ of 2-bromo-2-nitropropane-1,3-diol is higher than that of MCI. Several factors may account for this surprising result: bromo-2-nitropropane-1,3-diol is also used frequently in non-cosmetic applications (see below), and may be contained in protective creams that may have been used on compromised or even diseased skin (where the risk of sensitization is generally increased). In any case, the use concentrations may be too high in some or any of the applications, and should be reconsidered.

Altogether, there seems to be a good correlation between risk and hazard, at least on a rank scale (Table 3). However, risk can generally not be deduced directly from hazard, as the risk is influenced by exposure conditions. Despite the difference in potency between imidazolidinyl urea and MI (by a factor of 10), the similarity with regard to the SEQ may be explained by a too high exposure to formaldehyde (5, 12) via this formaldehyde-releaser. In contrast, hazard and risk correspond in the case of MI and iodopropynyl butylcarbamate (Table 3), whereas the SEQ (risk) in the case of MCI seems to be relatively low in view of the extreme hazard, probably owing to the previous adaptation of use concentrations to the extreme potency of MCI. In general, if a chemical of relatively low potency (according to the local lymph node assay) shows

Table 3. Comparison of sensitization exposure quotient (SEQ) (risk) and local lymph node assay (LLNA) data (hazard)

Preservative	SEQ	EC3%	EC3 ($\mu\text{g}/\text{cm}^2$)	References
Phenoxyethanol	0.06	ND	ND	
Benzyl alcohol	0.30	>50	>12 500	(24)
Parabens ^a	0.35	ND/>25/>50	—	(24–26)
Imidazolidinyl urea	1.6	24	5975	(27)
Methylisothiazolinone	1.7	1.9	475	(27)
Iodopropynyl butylcarbamate	3.4	0.87	218	(20)
Methylchloroisothiazolinone	9.0	0.05–0.009	2.25	(27, 28)
2-Bromo-2-nitropropane-1,3-diol	13	0.3 < (*) < 1	250	(29)

ND, no data.

(*): the (unknown) value between 0.3 and 1.0. The inverse correlation between SEQ and EC3 value (as % or $\mu\text{g}/\text{cm}^2$) is strong (Spearman correlation coefficient: -0.96 , exact $p = 0.0028$).

^aDepending on the molecule (methylparaben, ethylparaben, propylparaben, or butylparaben). *p*-Hydroxybenzoic acid, the free acid resulting from ester-cleavage of the parabens, was found to be a non-sensitizer (27).

a disproportionately high ranking in the SEQ (such as imidazolidinyl urea or 2-bromo-2-nitropropane-1,3-diol), this might indicate the need for critical review of exposure conditions (e.g. with regard to use concentrations).

One must conclude that hazard assessment alone for preventive purposes is only a first step, and must be supplemented by risk assessment based on exposure scenarios, if available, using human dose–response data from elicitation studies. However, the success (or failure) of such assessment always needs to be benchmarked against and, if necessary, corrected by the results of epidemiological surveillance in humans.

Limitations

This first attempt to relate allergy frequencies to preservatives and their use in cosmetics has important limitations:

- (1) Only leave-on products were considered, on the assumption that exposure to this product category is associated with a higher risk of sensitization (30), and only products were considered that (i) contained a substance that was patch tested (e.g. propionic acid was excluded) and (ii) were more often present in leave-products (>0.5%) (for example, methylidibromo glutaronitrile, formaldehyde, DMDM hydantoin and chloroacetamide were excluded).
- (2) The selection of products may not be sufficiently representative, despite the considerable number of products (>3000). A search in company websites in Sweden gave somewhat divergent results regarding the use of single preservatives, albeit on a much smaller sample size (204 cosmetics, 167 rinse-off products, and only 37 leave-on products) (31).
- (3) It cannot be excluded that if, in a few high-volume products, the preservatives contained deviate from the overall pattern, the representation of exposure to these preservatives will be distorted – namely, underestimated for those preservatives that are more commonly found in the high-volume products, resulting in a higher SEQ. Thus, the SEQ calculated here would reflect a ‘worst case’ situation.
- (4) Some preservatives are widely used in non-cosmetic areas, and sensitization may be acquired through these sources. However, the huge amounts of e.g. formaldehyde – it was contained in 2663 (mostly industrial) products registered by the Danish PROBAS register, with a total volume of 26153 tons/year [4] – gives no information at

all on the amount the skin is exposed to. Therefore, we excluded patients with occupational dermatitis from the analysis. However, occupational dermatitis may have remained undetected to an unknown extent, and this correction could therefore be insufficient, leading to an overestimation of the cosmetic-related risk. This may essentially be the case for preservatives that are widely used in industrial/non-cosmetic applications (e.g. paints/lacquers) (4, 32), such as iodopropynyl butylcarbamate, MCI/MI, bromo-2-nitropropane-1,3-diol, and MI. In contrast, these considerations would not apply to typical cosmetic preservatives, such as certain formaldehyde-releasers (32) or parabens. The diverging profiles of the MOAHLFA index (Table 1) may support the notion of a still quite heterogeneous exposure of the patients (see Results).

- (5) The case of bromo-2-nitropropane-1,3-diol may indicate that there may be factors other than cosmetic or occupational exposure leading to sensitization, such as an alternative exposure that has not been considered (topical drugs?) or a pre-existing inflammatory dermatosis (hand eczema), which is well known to increase the risk of sensitization.
- (6) Also regarding other allergens, our approach is necessarily limited by a partial mismatch of exposure data (which strictly refer to leave-on cosmetics) and sensitization data, as patients may be included who have been sensitized by preservatives from non-cosmetic sources, despite our attempts to reduce this problem by excluding patients with (probable) occupational dermatitis and patients with leg dermatitis exposed to a variety of topical preparations, respectively.

Conclusion

Sensitization risk is not necessarily reflected by the absolute or relative number of cases of sensitization. However, this can be – at least grossly – estimated by relating the relative frequencies of sensitization to the relative frequencies of use in products, serving as a marker of exposure. High sensitization prevalences may be put into perspective by a very high exposure. Therefore, parabens, with a sensitization frequency of >1%, appear to be associated with a low risk of sensitization. Other biocides, such as the formaldehyde-releasers, are associated with a moderate risk, whereas a further group (iodopropynyl butylcarbamate, MCI/MI, and bromo-2-nitropropane-1,3-diol) was identified as being associated with a higher risk in the SEQ-based ranking. Although there is no perfect correlation between risk and hazard (as expressed by sensitizing

potency according to local lymph node assay studies), substances found to pose a low risk were classified as weak sensitizers to non-sensitizers, and substances with a high risk were classified as moderate to strong sensitizers (Table 3), thus corroborating our approach of relative risk

assessment. The converse is also true: the hazard identified by predictive testing is obviously the most important (primary) determinant of risk, and may be compensated for only by adequately adjusted concentrations of exposure.

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