

Methylisothiazolinone is categorised as a strong sensitiser in the Murine Local Lymph Node Assay

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Methylisothiazolinone (MI) has a long history of use as a preservative in a mixture with the structurally related compound methylchloroisothiazolinone (MCI) in the ratio 1:3 MI:MCI. This mixture has high skin sensitization potency, MCI being the more potent. Replacement of the MI/MCI mixture by MI alone (since 2005, 100 ppm has been permitted in leave-on and rinse-off cosmetic products in the EU) has led to significant increases in reported cases of contact allergy and allergic contact dermatitis (e.g. 1, 2), raising the question of whether the sensitizing potency of MI has been underestimated. This editorial considers the potency of MI in the murine local lymph node assay (LLNA).

MI is widely quoted as being a moderate sensitizer (e.g. 3–5), in contrast to MCI which is quoted as strong or extreme, and the LLNA EC₃ value of MI is widely quoted as 1.9% (eg 6). This value is given in the 'Gold Standard' compilation of LLNA data published in 2005 (7). However, in a less widely quoted paper published in 2003 (8), the EC₃ value of MI is given as 0.4%, corresponding to categorisation as a strong sensitizer. The 'Gold Standard' value of 1.9% (7) is taken from a different 2003 publication (9) reporting modelling studies on a large set of LLNA data. In the light of the increase in consumer sensitization to MI, it is appropriate to analyse the discrepancy between the 2003 reported EC₃ value of 0.4% (8) and the 'Gold Standard' value of 1.9% (7).

The stimulation index (SI) values are the same from both references, and in both cases the vehicle was acetone/olive oil – so it seems safe to assume that the two publications are reporting the same test results. We see that in each case the concentrations are increased twice by a factor of 2, then by a factor of 2.5, then by a factor of 2 again. So it seems clear that the discrepancy between the two EC₃ values is related to a disagreement as to the MI concentrations tested.

The fifth column of the Table 1 lists the ratio of the concentration given in reference 8 to the concentration given in reference 7. This ratio is almost constant (the deviation probably results from rounding off) at 0.197, i.e. the reference 8 concentration is 19.7% of the reference 7 concentration.

Table 1. The table shows the dose response data as given in references 8 and 7 for MI in the LLNA

Reference 8 (2003)		Reference 7 (2005)		Concentration ratio
% MI	SI	% MI	SI	
0.049	1.5	0.25	1.5	0.196
0.099	1.5	0.5	1.5	0.198
0.197	1.8	1.0	1.8	0.197
0.493	3.8	2.5	3.8	0.197
0.985	2.5	5.0	2.5	0.197

A close reading of reference 8 reveals how the discrepancy must have come about. In reference 8 it is stated that the MI was in the form of a 19.7% aqueous solution. This solution was tested in the vehicle at 0.25%, 0.5%, 1%, 2.5% and 5%, corresponding to 0.049–0.987% concentrations of MI.

So now it seems clear what happened. The 19.7% solution having been tested at 0.5–5%, these concentrations were multiplied by 0.197 to give the MI concentrations, against which the SI values were plotted to give EC₃ value of 0.4% for MI, as reported in reference 8. The same 0.5–5% concentrations and corresponding SI values were reproduced in reference 9 and from that found their way into the compilation of reference 7, but in the process the fact that it was a 19.7% solution that had been tested was overlooked. Consequently the EC₃ value of 1.9% that is now widely quoted for MI applies to a 19.7% solution of MI, and the true EC₃ value for MI alone is 0.4%.

Thus MI is categorised as a strong sensitizer, not a moderate sensitizer, in the LLNA.

It is difficult to see how human errors of the type identified here can ever be completely avoided. There are probably other erroneous potency values in the literature. Bearing this example in mind, perhaps a good rule of thumb is that when a published potency value seems anomalous or inconsistent in light of other data, one should check the source of the biological data. Compilations of potency values are probably more likely to contain such errors than reports of testing on individual chemicals.

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