

CONTACT POINT

Ranking skin-sensitizing hair dye molecules according to their potency by the use of human cells

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The determination of the skin sensitization potential (potency) of hair dye ingredients without animal testing is crucial for their quantitative risk assessment. Besides *p*-phenylenediamine (PPD) and toluene-2,5-diamine (*p*-toluylenediamine [PTD]), which are 2 commonly used precursors and major allergens in oxidative hair dye-associated contact dermatitis,¹ >100 ingredients are currently used, including the precursor *p*-aminophenol.^{2–4} *p*-Aminophenol is used together with couplers such as 1-naphthol, *m*-aminophenol or resorcinol to create different shades.

Animal tests have indicated that *m*-aminophenol, *p*-aminophenol, 1-naphthol and resorcinol are contact sensitizers,^{1,5–10} being classified as strong contact sensitizers by the Scientific Committee on Consumer Safety.¹¹ However, whereas the precursor *p*-aminophenol and the coupler *m*-aminophenol frequently elicit patch test reactions in patch tested patients, with prevalences varying between 1.4% and 11%,^{12–14} patch test reactions to 1-naphthol or resorcinol are rare,^{1,10,15,16} although these couplers are also frequently used. Besides differences in exposure level and potential cross-reactivity patterns, differences in sensitization potency in humans may account for such different responses in patients.

We previously showed the capacity of our coculture model (COCAT) consisting of human cell lines, that is, HaCaT keratinocytes and THP-1 cells as surrogate dendritic cells, to rank PPD, PTD, and 2-methoxymethyl-*p*-phenylenediamine according to their potency based on the evaluation of the concentration inducing significant upregulation of the costimulatory molecule CD86 and/or adhesion molecule CD54 on cocultured THP-1 cells.¹⁷ Here, we studied the sensitization potency of *p*-aminophenol, *m*-aminophenol, 1-naphthol and resorcinol in this model.

METHODS

To assess the expression levels of CD86 and CD54 on cocultured THP-1 cells, THP-1 cells were exposed to *p*-aminophenol, *m*-

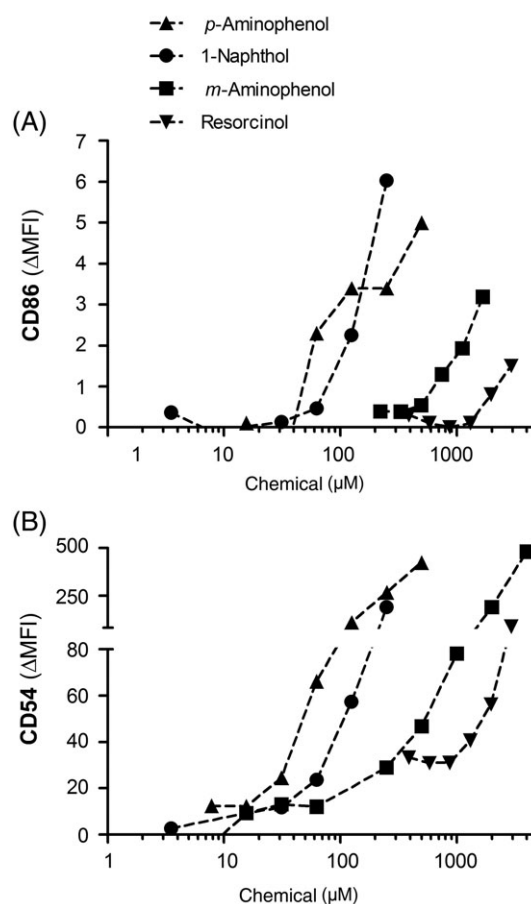


FIGURE 1 Comparison of the potential of the hair dye molecules *p*-aminophenol, 1-naphthol, *m*-aminophenol and resorcinol for activation of dendritic cells, measured as upregulation of CD86 and/or CD54 on cocultured THP-1 cells. THP-1 cells were exposed to chemicals in coculture with HaCaT keratinocytes for 24 hours, and upregulation of CD86 (A) and CD54 (B) was then analysed on viable THP-1 cells with flow cytometry (for each marker, 1 representative experiment from ≥ 3 is depicted). MFI, mean fluorescence intensity

TABLE 1 Comparison of COCAT results and potency derived from predictive animal tests

	COCAT ECA (mM, mean $\pm$ SEM, n $\geq$ 3)	Sensitization potency in predictive animal tests (expressed as EC3 in percentage derived from the local lymph node assay, if available)	References
<i>p</i> -Aminophenol	0.1 $\pm$ 0.03	Non-guideline guinea-pig tests indicate strong potency	9
1-Naphthol	0.2 $\pm$ 0.04	1.3	5
<i>m</i> -Aminophenol	0.6 $\pm$ 0.2	0.24; 3.2	8,20
Resorcinol	0.8 $\pm$ 0.3	1.4; 5.5	6,21

SEM, standard error of the mean.

aminophenol, 1-naphthol or resorcinol (Sigma Aldrich, Taufkirchen, Germany) in coculture with HaCaT cells for 24 hours. Expression of CD86 and CD54 on viable THP-1 cells (propidium iodide exclusion) was analysed with flow cytometry as described previously.^{17–19}

RESULTS

All chemicals upregulated CD86 and CD54 on cocultured THP-1 cells (Figure 1). However, slightly different concentrations were needed for upregulation of CD86 and/or CD54, showing the potency in vitro (designated as ECA, estimated via linear interpolation). Low test concentrations were sufficient for *p*-aminophenol, whereas those for 1-naphthol, *m*-aminophenol and resorcinol slightly increased, in this order (Figure 1).

DISCUSSION

Comparison of the present data with predictive animal tests shows that these reflect the differences in potency observed in vivo as shown in Table 1.

Beyond hazard identification, potency assessment is crucial for quantitative risk assessment of chemicals. However, existing human cellular models for analysis of sensitization potency provide only limited quantitative information as compared with our model. In this study, we evaluated 4 relevant molecules that are used in oxidative hair-colouring products, and found a good potency ranking reflecting in vivo results, supporting considerable sensitization potency for all studied hair dye molecules despite their varying clinical relevance. These data, together with our earlier results, show that this model can contribute to improving non-animal quantitative risk assessment for hair dye molecules, and thus may support the assessment of chemicals with limited or absent human sensitization data.

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Conflict of interest

The authors declare no potential conflict of interests.

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