

Risks of Allergic Contact Dermatitis Elicited by Nickel, Chromium, and Organic Sensitizers: Quantitative Models Based on Clinical Patch Test Data

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Risks of allergic contact dermatitis (ACD) from consumer products intended for extended (nonpiercing) dermal contact are regulated by E.U. Directive EN 1811 that limits released Ni to a weekly equivalent dermal load of $\leq 0.5 \mu\text{g}/\text{cm}^2$. Similar approaches for thousands of known organic sensitizers are hampered by inability to quantify respective ACD-elicitation risk levels. To help address this gap, normalized values of cumulative risk for eliciting a positive (“ $\geq +$ ”) clinical patch test response reported in 12 studies for a total of $n = 625$ Ni-sensitized patients were modeled in relation to observed ACD-eliciting Ni loads, yielding an approximate lognormal (LN) distribution with a geometric mean and standard deviation of $\text{GM}_{\text{Ni}} = 15 \mu\text{g}/\text{cm}^2$ and $\text{GSD}_{\text{Ni}} = 8.0$, respectively. Such data for five sensitizers (including formaldehyde and 2-hydroxyethyl methacrylate) were also $\sim$ LN distributed, but with a common GSD value equal to GSD_{Ni} and with heterogeneous sensitizer-specific GM values each defining a respective ACD-eliciting potency $\text{GM}_{\text{Ni}}/\text{GM}$ relative to Ni. Such potencies were also estimated for nine (meth)acrylates by applying this general LN ACD-elicitation risk model to respective sets of fewer data. ACD-elicitation risk patterns observed for Cr(VI) ($n = 417$) and Cr(III) ($n = 78$) were fit to mixed-LN models in which $\sim 30\%$ and $\sim 40\%$ of the most sensitive responders, respectively, were estimated to exhibit a LN response also governed by GSD_{Ni} . The observed common LN-response shape parameter GSD_{Ni} may reflect a common underlying ACD mechanism and suggests a common interim approach to quantitative ACD-elicitation risk assessment based on available clinical data.

KEY WORDS: Dose response; electronic wearable consumer products; metals; organic chemicals; skin sensitizers

1. INTRODUCTION

Allergic contact dermatitis (ACD) is a mild to severe “Type IV” or delayed, T-cell-mediated allergic skin reaction that follows (typically skin) exposure to an allergen. ACD involves three steps: (1) initial allergen contact that generates an asymptomatic sensitization (or induction or primary) phase of ACD in which dermal penetrated allergen molecules bind

to and covalently modify histocompatibility antigen proteins presented by and thus activate epidermal Langerhans cells (LCs); (2) those LCs migrate and activate allergen-specific T cells to proliferate and circulate systemically; and then (3) subsequent allergen contact in which the latter T cells interact with LCs newly activated by the same (or, in some cases, a chemically similar) allergen generate an elicitation (or secondary) phase of ACD involving cytokine-mediated dermal inflammation within 18–72 hours.⁽¹⁾ More than 4,450 ACD-eliciting organic chemical sensitizers are currently identified.^(2,3) ACD accounts for 90–95% of all occupational diseases and has an estimated $\sim 0.1\%$ average annual incidence rate among

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full-time workers, that is, approximately fivefold greater among hairdressers and barbers and most frequently involves sensitizers including some metals (e.g., nickel, chromium), some aromatic amines, and certain chemicals in epoxy/resin (e.g., formaldehyde and some acrylates and methacrylates), rubber, fragrances, cosmetics, and preservatives.⁽⁴⁾ In general populations of all age groups and all countries in Western Europe and North America between 1966 and 2007 who were patch tested with a standard series of test allergens, the estimated median percentage (and range) of those who respond with ≥ 1 positive reaction is 21.8% (11.8–35.4%) among females and 12% (6–18%) among males.⁽⁵⁾ For comparison, roughly the same and an approximately three- to five-fold lower general-population prevalence of Ni-specific ACD (as may be associated with exposure to jewelry from which Ni is released onto skin) occurred among women and men, respectively, and there was a ~ 2 –6% prevalence of allergic sensitivity to cosmetic or fragrance ingredients.⁽⁵⁾

Originally adopted in 1994 as the “Nickel Directive,” the European Commission (EC) EN 1811 standard^(6–9) for nickel-containing consumer items applies a 168-hour (one-week) leach-testing protocol and defines migration limits of 0.20 and 0.50 $\mu\text{g Ni/cm}^2/\text{week}$ for pierced-skin inserts and for other jewelry products, respectively, intended for direct and prolonged dermal contact. (To address measurement uncertainty, noncompliance with these limits was defined as of 2015 to occur only when measured Ni release is ≥ 0.35 or ≥ 0.88 $\mu\text{g Ni/cm}^2/\text{week}$, respectively.⁽⁹⁾) This nickel standard was subsumed since 2009 by European REACH regulations. To limit the risk of eliciting ACD in sensitized individuals handling cement and cement-containing preparations made using chromium (Cr) VI, E.U. regulations have since 2003 limited Cr(VI) concentrations in such products to ≤ 2 ppm of their total dry weight.⁽¹⁰⁾ To limit ACD-elicitation risk (ACDER) from Cr(VI)-containing leather consumer products that contact skin, E.U. REACH Regulation 301/2014 restricted the Cr(VI) content of leather products to < 3 ppm by weight as of May 1, 2015.⁽¹¹⁾ In 1999, the EC Scientific Committee on Cosmetic Products and Non-Food Products (SCCNFP) recommended consumers be warned if any of 26 specified fragrance allergens are present in cosmetic products; in 2003 the EC Scientific Committee on Cosmetic Products (SCCP) recommended 200 ppm as an upper limit of hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC) in such products; in 2009 the EC Regulation

1223 (Appendices II and III) banned a total of 1,370 substances and restricted 214 additional substances in cosmetic products; and in 2012 the SCCP recommended that among 82 established contact fragrance-allergens (54 chemicals and 28 natural extracts), dermal exposure via cosmetic products should not exceed 0.8 $\mu\text{g/cm}^2$ (or a Specific Concentration Limit of 0.01% per item), and that no level of the HICC, chloroatranol, or atranol fragrance is safe in such products.^(12–14) Additionally, the E.U. Dangerous Preparation Directive as amended classifies any concentration $\geq 1\%$ of any skin sensitizer ingredient as a skin-sensitizer hazard irrespective of potency and requires that any such concentration $\geq 0.1\%$ but $< 1\%$ must be declared on the product label even when the preparation is not classified as sensitizing.^(15,16)

Besides the regulations cited above, there currently are no regulations concerning exposures governing ACDER due to chemical sensitizers released onto skin from general consumer products, including a growing number of wearable-technology products. Complaints about allergic reactions attributed either to released nickel or to released residual methacrylate monomer from an adhesive component recently caused a product recall of a widely marketed electronic wearable product.⁽¹⁷⁾ The wearable-technology industry, currently valued at \$30 billion, is expected to grow to \$40 billion, \$100 billion, and \$150 billion by the years 2018, 2023, and 2026, respectively.⁽¹⁸⁾

With the primary exception of nickel as mentioned above, no widely accepted, validated methods currently allow quantitative ACDER assessments and comparisons that address all or most currently identified human sensitizers using methods validated against human patch test data, and this has been an active area of scientific development.⁽¹⁹⁾ Guinea pig tests (e.g., the guinea pig maximization test, the occluded path test, and the open epicutaneous test), the mouse local lymph node assay (LLNA), and human volunteer patch testing can all contribute to the assessment of relative sensitization potency, with LLNA being the most accessible method to generate *in vivo* experimental data for new chemicals of interest^(20–37) and the currently validated method of choice for sensitizer hazard identification and characterization.^(32,33,36) For example, quantitative log–log correlations (with R^2 values of ~ 0.75 – 0.80) are observed between “sensitization potency” estimates obtained from LLNA results (as “EC3” values representing concentration “thresholds” each estimated to yield a three-fold elevation above

measured background lymph-node proliferative activity), and those obtained from human repeated insult patch test (HRIPT) and/or human maximization test (HMT) results (as “threshold” concentrations estimated to elicit a sensitization reaction in 5% of tested individuals).^(22–26,29,31,33) Although advantageous compared to other sensitization tests because the LLNA provides quantitative end points, data characterizing dose–response relationships, and a proposed basis for “potency” prediction, applications of this assay remain focused on qualitative assignment of different tested chemicals into categories of (e.g., weak vs. moderate vs. strong vs. extreme) capacity to induce the sensitization phase of ACD.^(26,27,29,31,32,34) Data from *in vitro* assays can also be used to assess or classify skin sensitizing potency, such as the direct peptide reactivity assay of relative ability of chemicals to react with or modify skin proteins; *in vitro* (e.g., the human Cell Line Activation Test (h-CLAT)) assays of dendritic cell (DC) or DC surrogate cell surface marker induction; *in vitro* (e.g., KeratinosensTM) measures of oxidative stress-related Nrf2-mediated antioxidant response element activation or related keratinocyte or DC cytotoxicity or cytokine (e.g., IL-18) release; more recently developed Genomic Allergen Rapid Detection (GARD), EpiSenseA, SENS-IS assays of ACD-related gene expression, as well as quantitative structure–activity relationship (QSAR) modeling methods correlated with such *in vitro* measures and/or with *in vivo* (e.g., HRIPT or HMT) assays of sensitizing potency.^(26,28,32–34,36,37)

A fundamental limitation in applying such methods to quantitative ACEDR assessment is that they have as yet largely been validated against LLNA (and sometimes HRIPT or HMT) data pertaining to sensitizing potency, rather than to data characterizing potency to elicit ACD in already-sensitized individuals. Dose–response relationships for sensitization do not reliably predict allergen-specific or aggregate sensitizer exposures that unacceptably elevate risk of ACD elicitation *per se*,^(19,24,32,33,38–42) which typically is the more sensitive end point of clinical, industrial hygiene, and current/future regulatory concern.^(27,32,41,42) Epidemiological and clinical data thus continue to represent critical inputs to ACEDR assessment and management.⁽³³⁾

In the case of nickel—one of the best-studied contact allergens—a large amount of data generated in human patch test studies conducted over many decades supports the general conclusion that ACD elicited by Ni in Ni-sensitive patients has

a quasi-threshold, S-shaped (approximately logistic or lognormal [LN]) type distribution of cumulative sensitization likelihood as a function of Ni load applied.^(43,44) It is thus likewise unknown whether “threshold” concentrations estimated for sensitization by LLNA or HRIPT tests or for ACD by patch tests reflect any true slope discontinuity in low-dose dose response or rather merely reflect practical limitations on typical study size and power to discern low-dose dose–response patterns.

Efforts to limit ACEDR posed by dermal exposures to other metals and to semivolatile organic sensitizers (such as acrylate adhesive components of wearable products) are complicated in the absence of widely accepted, quantitative ACEDR assessment methods known to predict available human ACEDR data. To begin to address this gap, published ACD patch test concentration–response data for sensitized individuals were assembled, analyzed, and compared for three well-studied metallic ACD sensitizers, nickel, and chromium (VI and III), nine (meth)acrylate sensitizers (DiEGDMA, HEA, HEMA, HPMA, PEA, TetEGDMA, TetHFA, TriEGDMA, and TriMPTA), formaldehyde, two fragrance-related chemicals (HICC, used extensively in deodorants, and IG), and the preservative MDBGN. (Chemical acronyms used here are defined in Table I.) Data sufficient for dose–response modeling (for Ni, Cr(VI), Cr(III), PEA, formaldehyde, HICC, IG, and MDBGN) were, as shown below, all determined to have a similar (or in the case of chromium, partly similar) LN shape in relation to logarithmically scaled dermal load. Based on that similar shape, values of relative ACD-elicitation potency in relation to Ni were estimated for all seven of the other ACEDR-modeled sensitizers, and analogous potencies were estimated using more limited data available for each of nine (meth)acrylates. Based on these results, an interim general approach to quantitative ACEDR assessment is proposed and discussed.

2. METHODS

2.1. Clinical Patch Test Data

Study-specific sets of patch test data were obtained from the literature, each identifying minimally effective exposures in patients examined clinically after exhibiting ACD symptoms, initial patch testing indicating sensitization, and/or symptoms or (e.g.,

Table I. Metal and (Meth)Acrylate Data Sets and Relative Potency to Elicit ACD in Sensitized Individuals^a

Chemical	Acronym	CAS RN	MW (g/mol)	Number of Subjects, <i>N</i>	Average Load, <i>L</i> ($\mu\text{g}/\text{cm}^2$)	Number with $\geq +$ Test, <i>N</i> ₊	ACD Potency Relative to Ni, ϕ (Unitless)	References
Metals								
Nickel (ion)	Ni	7440-02-0	58.933	625	–	–	1	43,45–56
Chromium (VI) (ion)	Cr(VI)	7440-47-3	51.996	417	–	–	6.5 (1.7)	43,47,57–71
Chromium (III) (ion)	Cr(III)	7440-47-3	51.996	77	–	–	6.5 (2.5)	60,65
(Meth)acrylates								
Diethyleneglycol dimethacrylate	DiEGDMA	2358-84-1	242.268	23	2,000	14	0.012	72
2-Hydroxyethyl acrylate	HEA	818-61-1	116.13	485	36.8	45	0.033	73–76
2-Hydroxyethyl methacrylate	HEMA ^b	868-77-9	130.142	1,400 11 ^b	778 –	182 –	0.0019 1.0 ^b	73,75–80,82–85 81
2-Hydroxypropyl methacrylate	HPMA	923-26-2 27813-02-1.	144.168	531	750	103	0.0028	73,75,76,82,83
2-Phenoxyethyl acrylate	PEA ^c	48145-04-6	192.211	74 43 ^c	40 35.2	7 12	0.024 0.12 ^c	77,78,86 87
Tetraethyleneglycol dimethacrylate	TetEGDMA	109-17-1	330.373	33	1,467	12	0.0047	88–90
Tetrahydrofurfuryl acrylate	TetHFA	2399-48-6	156.179	2	80	2	>0.46	91
Triethyleneglycol dimethacrylate	TriEGDMA	109-16-0	286.321	762	851	93	0.0016	72–75,77–80,86,92–97
Trimethylolpropyl triacrylate	TriMPTA ^d	15625-89-5	296.316	754 47 4 ^d	38.2 80 7.1	14 5 3	0.0051 0.014 ^d 3.6 ^d	73,75–78,83,84,98 99 100
Other sensitizing chemicals								
Formaldehyde	FA	50-00-0	30.03	72	–	–	0.086	101–103
Hydroxyisohexyl 3-cyclo-hexene carboxaldehyde	HICC	31906-04-4	210.313	17	–	–	0.79	104,105

(Continued)

occupational) exposure history consistent with substantial risk of being sensitized to one or more dermal contact allergens. An administered mass or concentration of each tested chemical in aqueous concentration or mixed in petrolatum was extracted or derived from reported patch test information and expressed in corresponding units of minimal administered load (in $\mu\text{g}/\text{cm}^2$ of exposed forearm or back skin) determined to elicit an ACD reaction at least weakly positive in intensity using standard ACD-scoring criteria, as summarized in Table I. Patch tests done using Ni, Cr(VI), formaldehyde, HICC, IG, MDBGN, and (for certain patient subsets considered) HEMA, PEA, and TriMPTA all involved patients or study participants known or very likely to be sensitive to each respective agent based on previous test results or documented substantial occupational exposures (see Table I notes). Tests of Cr(III) were done on

those shown to have been sensitized to Cr(VI). All other (meth)acrylate-specific patch tests were done on patient groups reported to have been either occupationally or therapeutically exposed or (from previous patch test results) sensitive to ≥ 1 other tested (meth)acrylate (see Table I notes).

2.2. ACDER Models

Meta-analysis was used to combine and analyze clinical patch test data reported for Ni and for each of five organic sensitizers (formaldehyde, HEMA, HICC, IG, and MDBGN) for which published data were sufficient for dose–response assessment, as follows. For each sensitizer (*X*), combined data from all available studies were represented as *n* sets of the form $\{\ln(L_{X,i}), n_i\}$ relating the natural log of

Table I. Metal and (Meth)Acrylate Data Sets and Relative Potency to Elicit ACD in Sensitized Individuals^a

Chemical	Acronym	CAS RN	MW (g/mol)	Number of Subjects N	Average Load, L ($\mu\text{g}/\text{cm}^2$)	Number with $\geq +$ Test N_+	ACD Potency Relative to Ni, ϕ (Unitless)	References
Isoeugenol	IG	97-54-1	164.201	19	—	—	0.53	106,107
Methyldibromo glutaronitrile	MDBGN	35691-65-7	265.933	17	—	—	2.8	108

^aPatch tests done using Ni, Cr(VI), HICC, IG, and MDBGN listed here all involved patients sensitive to these agents, respectively, based on previous test results; tests of Cr(III) were done on those sensitive to Cr(VI); all (meth)acrylate-specific tests were done on patients known only to be sensitive to ≥ 1 (meth)acrylate, except as noted where chemical-specific sensitivity was known (see HEMA) or likely (see TMPTA, PEA). “—” indicates that data covering a broad range of dermal loads were modeled quantitatively (see Table II). Ni and Cr patch test data pertain to patients who previously tested positive to Ni and to Cr(VI), respectively. Isobornyl acrylate (not listed) was noted to elicit ACD in one case study but did not do so in any of a total of 153 patch tested patients and is not generally designated as a sensitizer.^(73,77,78,84) For each sensitizer X with a listed numeric load L , relative potency $\phi_X = \text{GM}_{\text{Ni}}/\text{GM}_X$ based on lognormal ACDEr model parameters listed in Table II. Parenthesized Cr-specific potencies were estimated using the conditional mixed-lognormal fits listed in Table II for Cr(VI) and Cr(III); otherwise, ϕ_X was estimated for each data set listed using Equations (3) and (4) (see Section 2).

^bPatch tests done on 11 patients sensitive to HEMA showed five positive reactions (i.e., a response rate of 5/11, or 45.5%) at a 0.02% (6.3 $\mu\text{g}/\text{cm}^2$) HEMA level⁽⁸¹⁾—significantly greater than the 158/1,236 (12.8%) rate observed in all patients sensitive or exposed to one or more (meth)acrylates^(73,75–80,82–85) excluding HEMA ($p = 0.015$, by Fisher’s exact test).

^cPatch tests done on 43 patients who worked with a polymer containing 88% PEA indicated 26 and 12 positive reactions at 1% and 0.1% (~ 352 and $35.2 \mu\text{g}/\text{cm}^2$) PEA levels, respectively⁽⁸⁷⁾—rates each significantly greater than the 7/74 (9.5%) response rate observed in patients allergically sensitive to one or more (meth)acrylates other than PEA^(77,78,86) ($p < 0.017$ and $< 10^{-8}$, respectively, by Fisher’s exact tests).

^dPatch tests done on four workers with “hand and face dermatitis after working with a floor coating containing as much as 3–5% TriMPTA” indicated 4 of 4 and 3 of 4 tests showing positive ACD reactions at 0.1% and 0.03% (24 and 7.1 $\mu\text{g}/\text{cm}^2$) TriMPTA levels, respectively⁽¹⁰⁰⁾—rates each significantly greater than the 14/754 (1.86%) response rate observed in patients exposed or allergically sensitive to one or more (meth)acrylates other than TriMPTA^(73,75–78,83,84,98) ($p < 10^{-4}$ and $< 10^{-6}$, respectively, by Fisher’s exact tests) and rates each significantly greater than the 5/47 (10.6%) response rate observed in workers exposed to TriMPTA in printing ink⁽⁹⁹⁾ ($p < 0.01$ and < 0.001 , respectively, by Fisher’s exact tests).

investigated dermal loads $L_{X,j}$ (expressed as μg X per cm^2 of exposed skin, as reported or inferred using other reported data) to corresponding total numbers n_j of observed ACD responses, each scored as exhibiting a severity characterized as at least “weak positive” (i.e., as $\geq +$) in different patch tested patients each already sensitized to X. For a few studies that omitted load or vehicle-mass information or references from which that information could be derived, loads were inferred based on an assumed mass of the reported vehicle (15 or 20 μg for petrolatum or aqueous vehicles, respectively). Resulting sets were sorted by ascending $L_{X,j}$ value, after which values n_i in each sorted set were transformed to corresponding normal (Van der Waerden) scores $Z_i = \Phi^{-1}(p_j)$, where: Φ = the cumulative standard normal distribution function; p_j = cumulative sample proportion ($\sum_{i=1}^j n_i)/(N+1)$, $j = 1, \dots, n$, associated with a combined total of N sensitized subjects tested from the combined set of X-specific studies; Φ^{-1} = the inverse of Φ ; and $\Phi^{-1}(p) = Z_p$ for proportions $0 < p < 1$. Each set of combined X-specific data was fit to a LN

probability model (see the Appendix) of ACDEr in relation to dermal load L_X :

$$R_X(L_X) = \Phi(\ln(L_X/\text{GM}_X)/\ln(\text{GSD}_X)), \quad (1)$$

where GM_X and GSD_X denote a geometric mean and geometric standard deviation estimated for sensitizer X, and $\ln$ denotes natural logarithm. Parameter estimates $\text{GM} = -(a/b)$ and $\text{GSD} = 1/b$ were obtained by unweighted least-squares (LS) linear regression (LR) to fit corresponding linear models $Z = a_X + b_X \ln(L_X)$ using *Mathematica* 11.0.1[®] software.⁽¹⁰⁹⁾ Resulting estimated slopes (b_X), and intercepts (a_X) conditional on a common estimated slope and corresponding GSD value ($\text{GSD}_X = \text{GSD}_0$ for all X), were assessed for homogeneity by corresponding nested F -tests from analysis of covariance for LR (ANOCOVAR), each yielding an $F_{df1,df2}$ statistic with $df1$ and $df2$ degrees of freedom.⁽¹¹⁰⁾ An approximate standard error (SE) of each reported GM and GSD estimate (EST) was estimated as the corresponding average relative deviation EST ($\text{RSE} + 1/\text{RSE}$)/2, where $\text{RSE} = \exp(\text{SD})$ and SD

is the standard deviation of each $\ln(\text{EST})$ estimate obtained from LS LR fits of the model $\ln(L_X) = \ln(\text{GM}_X) + \{\ln(\text{GSD}_X)\}Z_X$ to sensitizer-specific sets of transposed ACDER data $\{Z_X, \ln(L_X)\}$, from which it follows that $\text{RSE} = \{\gamma + (\gamma^2 + 4)^{1/2}\}/2$ where $\gamma = \text{SE}/\text{Est}$. A few excluded LR outliers were identified by nested F -test (see Table I notes).

Although somewhat more complex ACDER response patterns were observed for Cr(VI) and Cr(III), those patterns appeared to reflect a mixture of response characteristics including, for relatively sensitive sensitizer-specific subsets of individuals, an LN shape ($\text{GSD} = \text{GSD}_0$) common to the LN model fit (as discussed above) by ANOCOVAR to ACDER data for Ni and five organic sensitizers. To test this hypothesis, ACDER data for $X = \text{Cr(VI)}$ were modeled by iteratively reweighted LS nonlinear regression to fit a mixed LN (MLN) distribution:

$$R_X(L_X) = P\Phi(\ln(L_X/\text{GM})/\ln(\text{GSD}_0)) + (1 - P)F(\ln(L_X/\text{GM}_2)/\ln(\text{GSD}_2)) \quad (2)$$

using weights defined (to achieve slightly closer tail-specific fits) as $1 + \text{Abs}(Z_L)$ at each load L examined where $Z_L = \Phi^{-1}(R_X(L_X))$ using Equation (2). The much smaller set of ACDER data available for Cr(III) was modeled by fitting a constrained version of the MLN model defined by Equation (2) *conditional* on parameters GM and GSD_2 estimated for Cr(VI) (i.e., only two parameters P and GM_2 were fit to Cr(III) data). Goodness of fit by each estimated LN or MLN model was characterized heuristically by the corresponding explained fraction of total normalized response variance (R^2), in relation to a perfect fit indicated by $R^2 = 1$.

2.3. ACDER Potency Relative to Ni

Sensitizer- X -specific estimated parameters GM_X associated with corresponding LN $R_X(L_X)$ model fits obtained by ANOCOVAR as described above were (in view of observed slope homogeneity for Ni, five organic sensitizers, and to some extent Cr(VI) and Cr(III)—see Section 3) used to calculate values of relative ACD-elicitation potency ϕ_X defined as:

$$\phi_X = \text{GM}_{\text{Ni}}/\text{GM}_X \quad (3)$$

for each of five organic sensitizer sensitizers in relation to Ni. It follows that for all of these LN-modeled sensitizers, the following generalization:

$$R_X(L_X) = R_{\text{Ni}}(\phi_X L_X) \quad (4)$$

of the LN ACDER model defined by Equation (1) may be applied, in which potency-scaled load $(\phi_X L_X)$ represents a Ni-equivalent dermal load of sensitizer X . For comparison, alternative estimates of relative potency $\phi = L_{\text{Ni}}^*/R^{-1}(p^*)$ were calculated for Cr(III) and Cr(VI) based instead on corresponding estimated MLN risk models (see Equation (2)), where the implied Cr(VI) load $R^{-1}(p^*)$ was solved numerically, and where $p^* = R(L_{\text{Ni}}^*)$ denotes the ACDER level predicted for an EN 1811 limiting Ni load $L_{\text{Ni}}^* = 0.5 \mu\text{g}/\text{cm}^2$ by the Ni-specific LN ACDER model estimated as described above.

For nine (meth)acrylates patch tested at only a single reported load $L_{X,p}$ at which a number N_+ of “ $\geq +$ ” responders was reported among a total of N of patch tested individuals who had been sensitized as described in Table I, this information was used to estimate a corresponding responsive sample proportion $p = N_+/(N+1)$ from which a corresponding relative potency was estimated as:

$$\phi_X = (L_{X,p} \text{GM}_{\text{Ni}}) \text{GSD}^{Z_p}. \quad (5)$$

Equation (5) is implied by the generalized LN $R(\phi_X L_X)$ model defined by Equation (4) under the hypothesis that this model also pertains to each sensitizer X , the plausibility of which is suggested by results obtained in this study (see Sections 3 and 4). All calculations and plots were done using *Mathematica* 11.0.1[®] software.⁽¹⁰⁹⁾

3. RESULTS

Table II summarizes estimated LN model fits obtained for Ni, for five modeled organic sensitizers (based on ANOCOVAR), and for Ni and the five organic sensitizers using combined potency-scaled ACDER data, as well as estimated MLN model fits obtained for Cr(VI) and Cr(III). Using chemical-specific subject totals from Table I, Table II summarizes fits to patch test data reported for a total of 1,255 sensitized individuals. The LN model fit to Ni ACDER data is shown in Fig. 1. The LN fit to combined potency-scaled ACDER data for Ni and five organic sensitizers is shown in Fig. 2. Fig. 3 shows the estimated constrained MLN model fit to Cr(VI) ACDER data, conditioned on the ANOCOVAR-based GSD_0 estimate obtained for Ni and five organic sensitizers. Fig. 4 shows the constrained MLN model for Cr(III), fit conditional on the latter GSD_0 estimate and two additional parameters estimated for Cr(VI). All the estimated models summarized in Table II fit the respective modeled sets

Table II. Fits Obtained to Modeled ACD-Response Data

Sensitizer (X)	n	Estimated Lognormal-Type Model Parameter Values (± 1 SE) ^a					R^2
		p	GM ^b ($\mu\text{g}/\text{cm}^2$)	GSD ^b (Unitless)	GM ₂ ($\mu\text{g}/\text{cm}^2$)	GSD ₂ (Unitless)	
Cr(VI)	64	0.307 ± 0.0645	2.29 ± 0.588	[8.0]	17.2 ± 1.50	3.69 ± 0.277	0.993
Cr(III)	13 ^b	0.417 ± 0.0058	[2.29]	[8.0]	807 ± 63.2	[3.69]	0.988
Ni	78 ^c	—	14.9 ± 0.486	7.99 ± 0.193	—	—	0.988
Formaldehyde	6	—	$180. \pm 30.3$	7.99 ± 0.193	—	—	0.957
HEMA	4	—	14.9 ± 2.17	7.99 ± 0.193	—	—	0.986
HICC	10 ^c	—	18.9 ± 1.76	7.99 ± 0.193	—	—	0.975
IG	8	—	28.0 ± 3.12	7.99 ± 0.193	—	—	0.948
MDBGN	8 ^c	—	5.31 ± 0.541	7.99 ± 0.193	—	—	0.982
Combined ^d	114	—	14.9 ± 0.404	7.98 ± 0.194	—	—	0.985

^aSE = standard error; n = number of $\{\log(L), Z\}$ data points fit. See Table I for corresponding combined study population size (N) values; see Section 2 for model definitions.

^bANOCOVAR-based estimates of sensitizer-specific GM together with a common GSD are listed for each of six (noncombined) non-Cr sensitizers listed. GSD = GSD₀ = 8.0 value listed in brackets for Cr(VI) and Cr(III) was assumed based on the ANOCOVAR-derived common GSD estimate listed for all other sensitizers; GM and GSD₂ values listed in brackets for Cr(III) were assumed based on corresponding estimates listed for Cr(VI). Using subject totals listed in Table I, the Cr(VI) and Cr(III) fits were based on patch test data reported for a total of 494 sensitized individuals.

^cThe fit to Cr(VI) data excluded petrolatum (but not aqueous) vehicle data collected by Skog and Wahlberg⁽⁶⁹⁾ and K₂CrO₄ (but not K₂Cr₂O₇) data collected by Zelger and Wachter.⁽⁷¹⁾ The fit to Cr(III) data did not consider one quite disparate data set⁽⁶⁶⁾ (see text). Concerning the Ni data fit: geometric means of petrolatum and aqueous vehicle loads used by Emmett *et al.*⁽⁴⁸⁾ were used; numbers of positive reactions observed by Hindsén⁽⁴³⁾ and Hindsén *et al.*⁽⁵²⁾ among the same patients examined in each of four different seasons were averaged; similar averaging was done for similar response patterns observed by Wahlberg and Skog⁽⁵⁶⁾ using aqueous and petrolatum vehicles; and data from 5 Ni patch tests (involving 2 data points) were excluded as outliers ($p < 10^{-6}$).^(50,51) Data from one test each for HICC^(104,105) and MDBGN⁽¹⁰⁸⁾ were excluded as outliers ($p < 10^{-4}$).

^dData used for this analysis (not involving Cr(VI) or Cr(III)) were combined after adjusting sensitizer-specific loads L_X to corresponding values ($\phi_X L_X$) each scaled by a corresponding value of relative potency $\phi_X = \text{GM}_{\text{Ni}}/\text{GM}_X$ calculated using GM values listed above, yielding ϕ_X values listed in Table I. Using subject totals listed in Table I, the combined fit was based on patch test data reported for a total of 761 sensitized individuals.

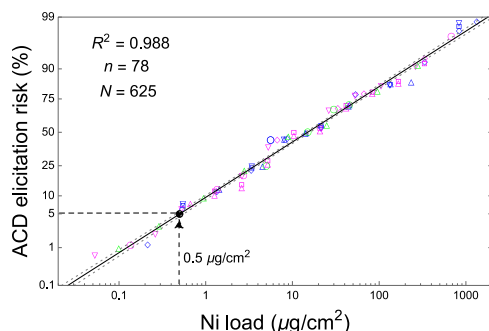


Fig. 1. Dose response for Ni-elicited ACD responses scored as weak positive (“+”) or greater measured in patch tests of $N = 635$ Ni-sensitive patients (yielding $n = 78$ cumulative response-likelihood points) fit to a lognormal (LN) model (solid line) with estimated parameters listed in Table II. Different point styles/colors signify data obtained from each of 12 different studies. Solid point indicates a reference dermal load of $0.5 \mu\text{g}/\text{cm}^2$ (corresponding to the EN 1811 standard).

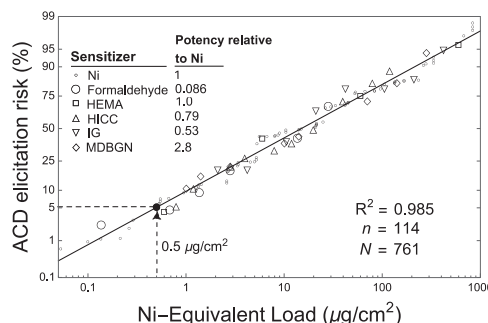


Fig. 2. Dose response for combined ACEDER data on Ni and five organic sensitizers (open points) using sensitizer-specific values of dermal load all scaled by corresponding ACD-eliciting potency (ϕ) relative to Ni ($n = \#$ of points fit, $N =$ total # patients studied) compared to a common lognormal (LN) ACEDER model fit (solid line) obtained by ANOCOVAR with estimated parameters listed in Table II. Solid point indicates the EN 1811 reference dermal load of $0.5 \mu\text{g}/\text{cm}^2$.

of ACEDER data reasonably well ($R^2 = \sim 0.95$ – 0.99 , Figs. 1–4).

Results from ANOCOVAR using six sensitizer-X-specific ACEDER data subsets (for $X =$ Ni, formaldehyde, HEMA, HICC, IG, and MDBGN)

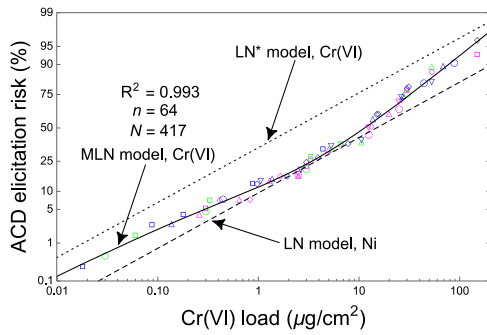


Fig. 3. Mixed lognormal (MLN) ACEDER model fit (solid curve) to Cr(VI) patch test data from 14 studies cited in Table I, shown using different point styles/colors (n = # of points fit, N = total # patients studied). Also shown are the lognormal (LN) model fit for Ni from Fig. 1 (dashed line) and the MLN model for Cr(VI) conditioned on $p = 1$ so as to represent the LN ACEDER model (LN*, dotted line) predicted by the Cr(VI)-MLN model to pertain to the most sensitive ~30% of all Cr-sensitized individuals.

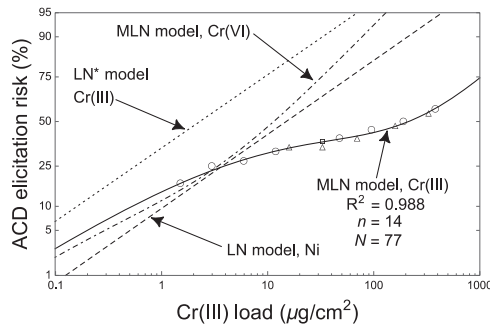


Fig. 4. Mixed lognormal (MLN) ACEDER model fit (solid curve) to patch test data from three studies cited in Table I shown using different point styles (n = # of points fit, N = total # patients studied). Also shown are the lognormal (LN) fit for Ni from Fig. 1 (dashed line), the MLN model fit for Cr(VI) from Fig. 3 (dot-dashed curve), and the MLN model for Cr(III) conditioned on $p = 1$ so as to represent the LN ACEDER model (LN*, dotted line) predicted by the Cr(III)-MLN model to pertain to the most sensitive ~42% of Cr-sensitized individuals.

indicated approximate equality of six corresponding estimated X-specific slopes (b_X) ($F_{5,102} = 0.90$, $p = 0.48$), but indicated significant inequality of corresponding X-specific intercepts (a_X) conditional on a common estimated slope (b) ($F_{5,107} = 111.5$, $p = \sim 0$). Table II lists corresponding ANOCOVAR-based estimates of the X-specific LN parameters GM_X and the common parameter $GSD_0 = \sim 8.0$ governing LN-distribution shape, calculated as described in Section 2. Table I lists corresponding estimated relative potencies (ϕ_X) for these six sensitizers calculated using Equation (3). In relation to Ni load

L_{Ni} , a corresponding estimated ANOCOVAR-based ACEDER model for Ni is given approximately by:

$$R(L_{Ni}) = \Phi(\ln(L_{Ni}/15)/\ln(8.0)). \quad (6)$$

This model implies that the EN 1811 reference limit of $L_{Ni}^* = 0.5 \mu\text{g}/\text{cm}^2$ on dermal Ni load is associated with an estimated ACEDER level of $p^* = R(L_{Ni}^*) = \sim 0.051$, that is, with an approximate 5% level of elicitation risk. In relation to the reference limit for Ni, L_{Ni}^* , a corresponding estimated ANOCOVAR-based ACEDER model for sensitizer X, is given approximately by:

$$R(L_X) = \Phi(\ln(\phi_X L_X/15)/\ln(8.0)). \quad (7)$$

Fig. 2 shows how this more general model is consistent with the combined set of potency-scaled ACEDER data for all six ACEDER-modeled sensitizers.

Under the hypothesis that this common model pertains to (meth)acrylate sensitizers generally, Equation (5) was applied to single, sensitizer-specific ACEDER data points each associated with more limited data (as listed in Table I) to estimate relative potencies for all nine listed (meth)acrylates. As expected, in the case of each of the three (meth)acrylates (HEMA, PEA, and TriMPTA) for which estimated potencies were calculated for different data subsets associated either with patients known or likely to have been sensitized to those specific sensitizers, or who instead were known only to have been sensitized or occupationally exposed to one or more (meth)acrylates, potencies estimated for the former group (all within ~10-fold that of Ni) were substantially greater than those estimated for the latter group (Table I).

A single relative potency value, $\phi_X = 6.5$, was calculated using Equation (3) for both Cr(VI) and Cr(III) based on (1) a GM parameter fit only to Cr(VI) data, and (2) an assumption (supported by good Cr-related fits conditional on this assumption noted in Table II) that the LN shape parameter $GSD_0 = \sim 8.0$ mentioned above also pertains to both Cr(VI) and Cr(III). However, the estimated MLN-model fits obtained for Cr(VI) and Cr(III) indicate (via corresponding estimated values of MLN parameter P) that the estimated common relative potency of 6.5 pertains only to relatively sensitive subsets consisting of ~31% and ~42%, respectively, of all tested Cr(VI)-sensitized patients (Table II). Somewhat smaller values of relative potency for Cr(VI) and Cr(III) that are also listed (in parentheses) in Table I were estimated directly from the complete

MLN fits obtained for these sensitizers, and thus pertain to all tested Cr(VI)-sensitized patients.

4. DISCUSSION

An LN model with a common shape parameter ($GDS_o = \sim 8.0$) was found adequate to characterize ACDER not only for Ni-sensitized patients exposed dermally to Ni, but also (in the potency-scaled form represented by Equation (4)) for patients sensitized to five different organic sensitizers for which sufficient data were available to characterize ACDER distributions quantitatively (Table II, Figs. 1 and 2). Using $\phi_{Ni} = 1$, this model predicts a 5.1% ACD response rate (p^*) among Ni-sensitized individuals to a Ni load equal to the EN 1811 reference limit (L_{Ni}^*) of $0.5 \mu\text{g}/\text{cm}^2$ for nonpiercing consumer products intended to have prolonged skin contact. This estimated rate is similar to the 5% response rate that was previously estimated to pertain to a Ni load of $0.44 \mu\text{g}/\text{cm}^2$ based on an average of logistic response models fit to data from eight studies of Ni-induced ACD.⁽⁴⁴⁾ Good fits were also obtained to Cr(VI)- and Cr(III)-specific sets of ACDER data using MLN models, each positing that for a relatively sensitive subpopulation ACDER is LN-distributed also with $GDS_o = \sim 8.0$ and with a single GM parameter that was fit only to Cr(VI)-specific data (Table II, Figs. 3 and 4).

Thus, a total of eight modeled sets of sensitizer-specific ACDER data from clinical patch tests done on sensitized individuals were each found to be fit reasonably well by LN response models, which in the case of chromium pertain to an estimated ~ 30 – 40% of relatively sensitive individuals. The fact that all of these models include a common estimated LN shape parameter ($GSD_o = 8.0$) suggests that quantitative ACDER characterization for all metallic and organic sensitizers could be performed using the general LN ACDER model given by Equation (7), at least in the absence of conflicting data and on an interim basis until more accurate methods become available. Such a model could be applied, for example, to set interim exposure limits as part of an overall regulatory or product-stewardship ACDER-management strategy implementing a consistent maximum-allowed ACDER response rate (p^*) for each sensitizer to which already sensitized individuals may be exposed, such as the $\sim 5\%$ rate implied by the EN 1811 standard for Ni, or some other ACDER rate(s) that may address the (typically small) prevalence of current sensitization among

occupationally or generally exposed populations, likelihoods of cross-reactions among sensitizers, and perhaps also cumulative-ACDER concerns. To facilitate such a strategy, note that the proposed model can be reexpressed to estimate cumulative ACDER to individuals exposed to n loads $L_{X_i} = \{L_{X_1}, L_{X_2}, \dots, L_{X_n}\}$ of n respective sensitizers X_i ($i = 1, \dots, n$), to each one of which each individual has already been sensitized, as:

$$R(L_{(X.)}) = \Phi(\ln([\sum_{i=1}^n \phi_{X_i} L_{X_i}]/15)/\ln(8.0)). \quad (8)$$

The estimated MLN Cr(VI) model contrasts with a less intuitive truncated-LN model used previously to characterize several individual ACDER data sets.⁽¹¹¹⁾ The difference between MLN-type ACDER models estimated for the complete Cr(VI) and Cr(III) data sets examined, compared to simpler and (shape-wise) similar LN models estimated for Ni and five organic sensitizers, may in part be attributable to inclusion of irritation responses together with ACD responses, particularly in the higher-load portion of the Cr(VI)- and Cr(III)-specific data sets modeled, in view of difficulty in distinguishing these two types of patch test reaction particularly in the case of Cr-associated ACD.^(57,58,62–64,66,111–114) This hypothesis is supported by the fact that the MLN models estimated for Cr(VI) and Cr(III) incorporate: (1) identical GSD_2 shape parameters, which under this hypothesis characterize the distribution of Cr-specific irritation responses observed at relatively higher Cr loads; and (2) the same GSD_o shape parameter estimated for Ni and five organic sensitizers, which under this hypothesis characterizes the distribution of Cr-elicited ACD responses.

Using more limited ACDER observations for nine (meth)acrylates, this proposed approach was illustrated by applying it, via Equation (5), to estimate corresponding values of ACD-eliciting potency relative to Ni, allowing corresponding interim quantitative ACDER estimates to be made for these sensitizers using Equation (6). The latter approach could also be applied using similarly limited sets of ACDER data available for some additional sensitizers.⁽¹¹⁵⁾ Alternatively, ACDER could be characterized more crudely by applying Equation (6) in which relative potency ϕ_X is estimated as the ratio of Ni-to-X-specific response levels from available HRIPT or HMT results at which 5% of those tested are estimated to be sensitized, or from LLNA test “EC3 threshold” results at which a three-fold sensitization-associated increase is estimated to

occur over background levels of lymphocyte proliferation. This cruder approach requires assuming that relative potencies for ACD elicitation are meaningfully estimated from corresponding relative potencies for sensitization, which could be tested by comparing potency estimates obtained by this method to corresponding estimates of elicitation potency listed in Table I. For example, such HRIPT/HMT estimates obtained for Ni, formaldehyde, and IG were recently estimated⁽³¹⁾ to have geometric mean (GM) values of 27, 191, and 1,016 $\mu\text{g}/\text{cm}^2$, respectively, implying (via the HRIPT/HMT method) that $\phi = 0.14$ for formaldehyde and $\phi = 0.027$ for IG. While the HRIPT/HMT-based potency estimate for formaldehyde is $\sim 64\%$ greater than the corresponding estimate $\phi = 0.086$ listed in Table I based on applying the proposed LN AC DER model, the HRIPT/HMT-based estimate for IG is ~ 20 -fold less than the corresponding estimate $\phi = 0.53$ listed in Table I. Note that the estimated 27- $\mu\text{g}/\text{cm}^2$ GM value of Ni load associated with a 5% positive HRIPT/HMT-measured sensitization-response likelihood exceeds by >50 -fold the corresponding load ($L_{\text{Ni}}^* = 0.5 \mu\text{g}/\text{cm}^2$) noted above to be associated with approximately the same AC DER-response likelihood, illustrating quantitatively the well-recognized fact that sensitization typically requires far greater dermal loads to induce than do those required to elicit ACD.

Alternatively, ϕ_X can be estimated (albeit again crudely) as the Ni-to-X ratio of (e.g., minimum or median) test concentrations that are commonly recommended or commercially distributed to dermatologists to conduct clinical ACD patch tests, as listed for many hundreds of contact allergens in dermatology reference databases.^(2,116) For example, this “concentration method” of estimating ϕ_X can be illustrated using the following sensitizer-specific minimum recommended or distributed concentrations (as % by weight, typically prepared in petrolatum):⁽¹¹⁶⁾ Ni (2.5%), Cr(III) (0.5%), HEMA (1%), TMPTA (0.1%), formaldehyde (1%), HICC (5%), IG (1%), and MDBGN (0.2%). By this method, these patch test concentrations imply the following respective ϕ_X estimates, here each followed by the magnitude (rounded to two digits) of the relative difference between this estimate and the maximum corresponding estimate listed in Table I based on analysis of patch test data in individuals sensitized to the tested chemical: Cr(III) (5.0, 1.3), HEMA (2.5, 2.5), TMPTA (25, 6.9), formaldehyde (2.5, 29), HICC (0.5, 1.6), IG (2.5, 4.7), and MDBGN (12.5, 4.5). Thus, the “concentration method” of potency estimation here yielded six

of seven potency estimates that agree within sevenfold of the LN-regression-based estimates listed in Table I, but also yielded a formaldehyde potency estimate that is ~ 30 -fold greater than the corresponding estimate derived by analyzing patch test data obtained for formaldehyde-sensitized individuals.

The distribution of AC DER-response likelihoods is thought to reflect a combination of immunologically preserved memory of the intensity of an initial sensitizing exposure, and genetically driven interindividual variability in immunological sensitivity or predisposition toward subsequent triggers of T-cell-mediated ACD elicitation.^(117–122) The remarkable similarity of AC DER distribution shapes observed for Ni and five organic sensitizers, and to at least some extent for Cr(VI) and Cr(III), may reflect a prior sensitizing exposure-magnitude/exposure-frequency scenario and a common requirement for transduction and integration of information from perhaps just a few activated receptors to elicit an ultimate ACD-elicitation response. For example, if ACD elicitation were to require the joint occurrence of just three such events each typically characterized by $\sim$ LN-distributed interindividual variability, two with GSD = 3 and one with GSD = 4, then AC DER would have an expected $\sim$ LN distribution with $\text{GSD} = \exp\{2 \ln(3)^2 + \ln(4)^2\}^{1/2} = \sim 8.02 \approx \text{GSD}_0$. The approximate lognormality of the modeled AC DER data sets observed in this study (in the case of chromium, pertaining to estimated relatively sensitive patient subsets) appears to challenge the traditional assumption that “thresholds” exist for ACD-elicitation response relationships, and is consistent with previous observations that such thresholds often fail to be evident when analyzing sets of concentration-series patch test data large enough to measure relatively low rates of positive response to relatively small dermal loads.⁽⁴²⁾

5. CONCLUSION

Clinical patch test data characterizing ACD elicitation after controlled dermal exposure to specific dermal loads (in units of applied mass per unit skin area) of a well-studied sensitizer (nickel, chromium VI, chromium III, or one of the five organic sensitizers: formaldehyde, HEMA, HICC, isoeugenol, or MDBGN), were collected from previously published concentration series studies involving a total 1,255 sensitized individuals. It was discovered that the relationship between the likelihood of ACD elicitation after exposure to nickel, to each of the five organic

sensitizers, and to either species of chromium at least for a substantial fraction of (comprising the most sensitive) exposed individuals, is approximately log-normally distributed in relation to dermal load. Notably, although the fitted LN distributions of ACD elicitation response each have sensitizer-specific values of estimated “potency” (or geometric mean dermal load), all the estimated response distributions have approximately equal values of the parameter governing LN shape (i.e., geometric standard deviation). This means that, at least for these relatively well-studied sensitizers, ACD elicitation risk after exposure to any (patch-test-equivalent) dermal load of a specific sensitizer can be estimated directly from the value of its “potency” parameter (or from its value relative to that of any selected index sensitizer such as nickel). This also implies that aggregate elicitation risk following concurrent dermally localized exposure to multiple sensitizers can easily be calculated by evaluating the unified LN risk model in relation to a sum of potency-weighted dermal loads.

Whether the LN model of ACD elicitation risk in relation to dermal load identified here for eight of the most well-studied sensitizers examined via clinical patch testing to date pertains to any, most, or all of the thousands of human skin sensitizers identified to date remains unknown. This is due to absence or lack of sufficient data reported from clinical studies involving a sufficient series of patch test concentrations performed on sufficient numbers of sensitized patients for the vast majority of these sensitizers. However, the common risk model found to apply to all eight of the well-studied skin sensitizers examined here suggests that this model may serve as a reasonable default assumption to apply generally for all human skin sensitizers, pending development of one or more accurate approaches to predict ACD elicitation risks. Advantages offered by this approach include: its basis derived exclusively from clinical patch test data; its focus on quantitative characterization of risk associated with the most sensitive, symptomatic phase of ACD (elicitation) among already sensitized individuals, rather than on characterizing capacity to trigger the less sensitive initial asymptomatic (sensitization or induction) phase of ACD; its ability to infer aggregate risk associated with joint localized exposure to multiple sensitizers; and its ability to derive at least a crude estimate of ACD elicitation potency and exposure-specific risk for any sensitizer with only very limited available patch test data (e.g., involving only a single value of dermal load applied to at least several individuals). The latter advantage

was illustrated in this study by applying the risk model to estimate values of elicitation potency (relative to that of nickel) for each of nine (meth)acrylates using patch test data obtained for more than 4,000 patients who exhibited sensitivity to one or more (meth)acrylates.

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APPENDIX: NORMAL AND LOGNORMAL PROBABILITY MODELS

The bell-shaped, standardized symmetrical Gaussian or “normal” probability model plays a key role in probability and statistical analysis. This is because the Central Limit Theorem shows that this specific bell-shaped curve represents the probability (denoted $\text{Prob}(Z = z)$) that a sample average value $\hat{X} = \sum_{i=1}^n X_i/n$ of n independent random samples or measures X_i ($i = 1, \dots, n$) of an identically distributed random variable X , reexpressed as a standardized deviation $Z = (\hat{X} - \mu)/\sigma$ from the expected value μ and variance σ^2 of $\hat{X}$ (equal to the expected value μ and variance $n\sigma^2$ of X), equals a particular deviation magnitude z in the limit asymptotically as n becomes infinitely large, and approximately so even if n is moderately large.⁽¹²³⁾ Thus, any normally distributed variable X can be reexpressed as a similarly standardized variable $Z = (X - \mu)/\sigma$ in relation to the expected value μ and variance σ^2 of X . The corresponding bell-shaped normal probability $\text{Prob}(Z = z)$ has a peak probability (or maximum-likelihood) value when $X = \mu$. The corresponding S-shaped cumulative standard normal probability function, $\text{Prob}(Z \leq z) = \Phi(z)$, sums the area (i.e., values of probability p) under the bell-shaped $\text{Prob}(Z = z)$ curve, increasing from $p = 0$ to 0.5 to 1 as the standardized deviation z increases from $-\infty$ to 0 to ∞ , respectively. Values of the distribution function $\Phi(z)$, and of its inverse $\Phi^{-1}(p)$, are tabulated in relation to z and p in statistical

reference books, and can be calculated using statistical software (e.g., by evaluating NORM.S.DIST(z , True) and NORM.S.INV(p), respectively, in Microsoft Excel®). If X is a normally distributed random variable and $Y = \log(X)$, then the probability model for Y and $\log(X)$, called a lognormal distribution, is governed by parameters μ and σ described above, but that in this case can be expressed alternatively as a geometric mean (GM) $\exp(\mu) = e^\mu$ and geometric standard deviation $\exp(\sigma) = e^\sigma$, respectively, where Euler's constant e denotes the base of the natural logarithm. The lognormal probability model is applied to describe variability and/or uncertainty associated with positive-valued measurements pertaining to a wide variety of natural physical, meteorological, astronomical, chemical, and biological phenomena.^(124–128)

Ordered (i.e., sorted least-to-greatest) sample values X_i ($i = 1, \dots, n$) of a normally distributed random variable X can be used to construct an empirical cumulative distribution function connecting the points $\{Z_i, X_i\}$, each of which involves a Van der Waerden score $Z_i = \Phi^{-1}(p_i)$ defined as a function of a corresponding cumulative sample proportion (or “fractile”) $p_i = i/(n + 1)$; LR of X_i on Z_i then yields a 0-intercept and slope that robustly estimate the parameters μ and σ , respectively, of the normal distribution that models random variation in realized measures of X .^(123,129)

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