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Letter to the Editor

Use of Dermal LD_{50} as a Criterion for Skin Notation

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Dear Dr. Pierce,

We read with interest the recent article by Czerczak and Kupczewska entitled "Assignment of Skin Notation for Maximum Allowable Concentration (MAC) List in Poland" in the March 2002 issue of *Applied Occupational and Environmental Hygiene*.[1] Czerczak and Kupczewska analyzed the organic chemicals from the Polish MAC list for skin notation (the *Sk* index) and concluded that "... the dermal dose LD_{50s} [lethal dose 50 percent] determined on experimental animals ought to be adopted as the fundamental criterion for providing a substance with the percutaneous absorption notation in the MAC list."

We would like to comment on the need for a careful analysis of the data underlying a dermal LD_{50} or an occupational exposure limit (OEL) before using either of them to assess the appropriateness of a dermal hazard notation.

Selection and Coding of a Dermal LD_{50} Value

The authors introduced an analysis to investigate the correlation between chemicals with *Sk* notations included on the current Polish MAC list and the dermal LD_{50} values for these chemicals. The analysis involved two steps. First, as stated in the article, the authors "procured LD_{50s} data for the 195 TLV® List (ACGIH®) chemicals from the *Registry of Toxic Effects of Chemical Substances*" (*sic*). The authors grouped the 195 substances into five coded toxicity categories, with the top three categories being *extremely toxic* ($LD_{50} < 20$ mg/kg), *highly toxic* (20–200 mg/kg), and *moderately toxic* (200–5,000 mg/kg). Next, the authors used a mathematical formula to "relate the probability of chemical substance *Sk* notation in the MAC list with the dermal toxicity code." It is not clear what values the authors compared or which "195 TLV® List (ACGIH®) chemicals" they used as a base. However, the chemicals appear to be the 195 substances that have established ACGIH® TLVs® as well as dermal LD_{50} values published in the *Registry of Toxic Effects of Chemical Substances* (RTECS) in 1988, as reported by Kennedy et al.[2] This presumption is supported by the fact that the probability data reported by Czerczak and Kupczewska are the same as those reported by Kennedy et al.

Kennedy et al. suggested that all chemicals with LD_{50} values below 1000 mg/kg should initially be assigned a skin notation until more definitive work proves otherwise. The authors noted that the Group of Experts for Chemical Agents in Poland proposed that "all chemicals with [dermal] LD_{50s} value below 1000 mg/kg should be provided with the *Sk* index in the MAC list."

In our experience, the success of the above approach depends on the reliability and consistency of dermal LD_{50} values as a quantitative indicator of the systemic toxicity resulting from skin exposure. In practice, the dermal LD_{50} values reported for a chemical substance from studies employing different designs or animal species can vary significantly, and the cause of animal death as reported may not distinguish whether the fatalities result from systemic toxicity due to skin absorption or from corrosive effects at the site of administration.

The following examples illustrate some of the difficulties in interpreting LD_{50} values based on empirical data. The insecticide diazinon (CAS 333-41-5), as summarized in RTECS, has dermal LD_{50} values of 180, 633, 2750, and 3600 mg/kg for rats, pigs, mice, and rabbits, respectively.[3] If we follow the toxicity coding system the authors outlined, diazinon can be classified either as a *highly toxic* or a *moderately toxic* compound, and can be awarded or denied an *Sk* symbol, depending on the dermal LD_{50} used to reach the decision. Other examples include ethylene chlorohydrin (CAS 107-07-3), methyl parathion (298-00-0), phorate (298-02-2), ethion (563-12-2), and chlorpyrifos (2921-88-2). These compounds all have significantly different dermal LD_{50} values (as reported in RTECS), and the dermal LD_{50} values for each of these compounds fall into different categories of the toxicity coding system described above.

Another source of uncertainty about the quality of dermal LD_{50} data is the period of exposure adopted in laboratory experiments. The exposure protocol is frequently not included in the dermal LD_{50} reports in the secondary literature such as RTECS. Most studies yielding dermal LD_{50} values involve short exposure times, often a single exposure, and very short follow-up observations (often less than 48 hours). These typical dermal LD_{50} study protocols may not capture chronic effects such as cancer or reproductive effects. The dermal LD_{50} values are often based on acute effects that render them inappropriate indicators of detrimental effects of long-term exposure. An example is vinyl cyclohexene dioxide (VCD; CAS 106-87-6). VCD has reported dermal LD_{50} values of 620 μL/kg in rabbits[3] and 3216 mg/kg in mice.[4] Both values are considered to be only moderately toxic following the authors' toxicity coding system. However, VCD induces skin tumors in rodents from chronic dermal exposures (5 days per week for 103 to 105 weeks).[4] Chronic effects from long-term exposures to hazardous substances

at low concentrations are a growing occupational health concern. Dermal LD_{50} values determined on the basis of acute exposures may not provide adequate and necessary information for protecting workers' health.

Other factors that may contribute to the uncertainty of dermal LD_{50} values from animal studies include the sensitivity of tested animal species and the concomitant exposure to solvent vehicles. The presence of solvents in a mixture may enhance the skin permeation of the tested compounds.[5] All these experimental variables potentially reduce the accuracy and consistency of empirical data. Therefore, the use of dermal LD_{50} values requires a careful analysis of data to ensure the quality of data and the validity of results for interpreting systemic toxicity.

Mathematical Determination of Dermal Absorption/Toxicity Potential

Czerczak and Kupczewska also presented a mathematical method designed by Fiserova-Bergerova et al.[6] to determine the dermal absorption of chemical substances for the purpose of *Sk* assignment. In this method, the *Sk* assignment is determined by relating the chemical dose estimated to be due to dermal absorption to a calculated reference dose based on inhalation uptake at the OEL. The authors also presented a discussion of the Dutch Expert Committee on Occupational Standards based on a similar strategy. This strategy has its limitations: It depends on the reference dose, which in turn depends on the OEL. OELs may be set by analogy, and they may have significant safety factors incorporated into their derivation. Many OELs are simply based on skin, eye, or respiratory tract irritation. These OELs may result in reference doses that are not appropriate bases for determining the systemic effects from dermal absorption.

Conclusions

Dermal LD_{50} data are often inconsistent and dependent on study protocols, and the supporting studies are normally conducted in a manner that yields only acute toxicity data. The dermal LD_{50} is useful as an indicator for occupational health risk only when the health effects of a substance are limited to acute effects. Mathematical methods for estimating the health risks posed by skin absorption of chemical substances are also subject to limitations when used as the single tool in the risk assessment process. As noted above, determining an appropriate reference dose requires a thorough analysis of the data supporting the OEL.

An additional approach that may be considered for screening chemical substances is the parallel use of a validated mathematical model for estimating dermal absorption and the dermal LD_{50} information. The use of such an approach is currently the goal of our own interest. This approach preserves the simplicity of using dermal LD_{50} values as a quantitative measure, yet it incorporates the stability of a modeling approach. The approach also circumvents the difficulty in translating laboratory observations of toxic effects in studies with different design protocols. This approach may be a useful tool in adjusting for the observed variations in reporting and calculating dermal LD_{50} values, variations in criteria for assigning skin notations, and variations in standards for developing OELs.

In this approach, a mathematical model predicting dermal absorption risk is first "calibrated" with chemical substances known to promote systemic toxicity via skin absorption. Through the calibration process, the model variables (e.g., the amount of a chemical that must be absorbed through skin to constitute a health risk) will be properly defined. The model can then be used in addition to dermal LD_{50} values and other relevant information to assess the risk of skin exposure. The modeling results and the dermal LD_{50} for a chemical may not always agree. However, the disagreement provides a safeguard to alert the risk assessors that further analysis is necessary to fully quantify the risk; for example, determining whether the LD_{50} values of the evaluated chemical are based on systemic or local corrosive effects, or whether the OEL is based on systemic effects or local irritation.

Additional investigations will allow proper analysis and verification of information from the screening processes. These efforts will generate important information and contribute to producing systematic estimates of dermal toxicity for substances that have been inadequately evaluated. These investigations should benefit workers as well as occupational safety and health professionals who are considering dermal risks and the need for protection against the potential effects of hazardous materials.

Respectfully,

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and Heinz W. Ahlers, J.D.

REFERENCES

1. Czerczak, S.; Kupczewska, M.: Assignment of Skin Notation for Maximum Allowable Concentration (MAC) List in Poland. Appl Occup Environ Hyg 17(3):187–199 (2002).
2. Kennedy Jr., G.L.; Brock, W.J.; Banerjee, A.K.: Assignment of Skin Notation for Threshold Limit Values Chemicals Based on Acute Dermal Toxicity. Appl Occup Environ Hyg 8(1):26–30 (1993).
3. National Institute for Occupational Safety and Health: Registry of Toxic Effects of Chemical Substances (RTECS) Database. CD-ROM. NIOSH, Cincinnati, OH (December 2001).
4. National Toxicology Program: Toxicology and Carcinogenesis Studies of 4-Vinyl-1-Cyclohexene Diepoxide (CAS No. 106-87-6) in F344/N Rats and B6C3F1 Mice (Dermal Studies). NTP Technical Report Series No. 362. DHHS (NIH) Pub. No. 90-2817. National Technical Information Service, Springfield, VA (1989).
5. Watkinson, A.C.; Joubin, H.; Green, D.M.; et al.: The Influence of Vehicle on Permeation from Saturated Solutions. Int J Pharm 121:27–36 (1995).
6. Fiserova-Bergerova, V.; Pierce, J.T.; Droz, P.O.: Dermal Absorption Potential of Industrial Chemicals: Criteria for Skin Notation. Am J Indus Med 17:617–635 (1990).

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