MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

June 28, 1999

TO: File for lactic acid (50-21-5)

FROM: Dan O'Brien, Toxics Unit

SUBJECT: Initial Threshold Screening Level

The initial threshold screening level (ITSL) for lactic acid is 7 µg/m^3 based on an annual averaging time.

The following references or databases were searched to identify data to determine the ITSL: AQD chemical files; EPA's Integrated Risk Information System (IRIS) and Health Effects Assessment Summary Tables (HEAST); American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value (TLV) Booklet; National Institute for Occupational Safety and Health (NIOSH) Pocket Guide to Chemical Hazards and Registry of Toxic Effects of Chemical Substances (RTECS); National Toxicology Program (NTP) World Wide Website (WWW), MDEQ Library; International Agency for Research on Cancer (IARC) WWW; Chemical Abstract Service (CAS) On-line and National Library of Medicine (NLM) Toxline (1967–April 14, 1999), Chemical Evaluation Search And Retrieval System (CESARS), Handbook of Environmental Data on Organic Chemicals, Patty's Industrial Hygiene and Toxicology, Merck Index and the Condensed Chemical Dictionary.

Lactic acid is a colorless to yellowish, odorless, hygroscopic syrupy liquid. It has commercial applications in the production of dairy products and chemicals (salts, plasticizers, adhesives, pharmaceuticals, lactates); as an acidulant; as a mordant in wool dyeing; and as a general purpose food additive (Hawley, 1981). It is a normal metabolite in the physiological reactions of humans and other mammals, and is generally recognized as safe (GRAS) as a food additive (Clary *et al.,* 1998).

Despite its common use and its occurrence in metabolic reactions, surprisingly little toxicological information is available for lactic acid. With respect to acute exposure, Lethal Dose $(LD)_{50}$s have been determined in both rats and guinea pigs (Smyth *et al.*, 1941). Those authors used groups of 10 male albino Wistar rats, or groups of 10 strain-unspecified guinea pigs of mixed gender. The rats typically weighed between 90 and 120 g, and the guinea pigs between 250 and 300 g. Lethal doses and associated confidence intervals were calculated by the method of probits. The LD_{50} (95% confidence limits) were found to be 3.73 (3.02, 4.61) g/kg in rats, and 1.81 (1.69, 1.93) in guinea pigs. In both cases, the exposures were by single dose gavage. Other

summary references to acute toxicity which could not be independently verified by consulting the original study include oral LD_{50}s of 3543 mg/kg in rats, >2250 mg/kg in quail (Farm Chemicals Handbook, 1991), and 4875 mg/kg in the mouse (RTECS, 1999), as well as a dermal LD_{50} of >2 g/kg in the rabbit (Farm Chemicals Handbook, 1991). No acute inhalation studies with lactic acid were located in our searches.

Chemical Abstract Service searches referred to an extensive cosmetic ingredient review that incorporated some information concerning lactic acid (Anonymous, 1998). While that reference could not be obtained for review, the abstract suggests that repeat insult skin patch tests for lactic acid were negative and that lactic acid was expected to be a minimal to moderate ocular irritant. Recently, another review has been published on the safety of the esters of lactic acid (Clary *et al.,* 1998). It concludes that lactic acid and aliphatic alcohols are the likely metabolic products of esterase activity in the body and, thus, turns some attention to the toxicity of lactic acid. It concludes that minimal systemic toxicity from exposure to lactic acid is likely "because lactic acid is a normal metabolic product in humans." This contention is supported by a 13-month drinking water tumorigenicity study of lactic acid in rabbits, a teratogenicity study of lactic acid in mice, and a 2-year drinking water tumorigenicity study of calcium lactate in rats, all of which were apparently negative[1]. Clary and associates go on to conclude that "lactic acid toxicity is primarily related to its acidity." Thus, irritation seems likely to be the critical effect of inhalation exposure, calling into question the appropriateness of using oral data to derive a screening level.

While not available for lactic acid, inhalation toxicity data are available for some of the lactate esters. Four-hour Lethal Concentrations 50 (LC_{50}s) of the methyl, ethyl, butyl, isobutyl and isoamyl lactate esters were all in excess of 4g/m^3 (4,000,000 μg/m^3). Clary *et al.* (1998) stated that "no mortality was noted in (these) acute inhalation toxicity tests", suggesting that the LC_{50}s listed were actually insufficient to cause lethality. In addition, 28-day repeat inhalation toxicity tests have been carried out for vapors of the ethyl, *n*-butyl, isobutyl and 2-ethylhexyl esters, and for aerosols of the 2-ethylhexyl ester. Five male and five female rats per exposure level (for the ethyl, isobutyl and 2-ethylhexyl [vapor] esters), or six males per exposure level (for the *n*-butyl ester and a supplementary [aerosol] study of the 2-ethylhexyl ester) were exposed 6 hours per day, 5 days per week. Physiological parameters monitored included body and organ weights, food consumption, hematology, serology, and gross and histopathology. No hematology or serology measures were made in studies of *n*-butyl lactate or the supplemental study of 2-ethylhexyl lactate.

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[1]Only one of these studies (the chronic rat study) was potentially available for our review. Because the agent studied was calcium lactate (rather than lactic acid), questions have been raised as to its direct relevance for the derivation of a screening level for lactic acid. The other studies are noted by the review as cited in an unavailable Cosmetics Ingredient Review (1997), which, judging by its citation, appears to have been the basis of Anonymous (1998). That reference, too, was unavailable for review.

- In two separate studies of ethyl lactate, rats were exposed to exposure concentrations of 0, 150, 600, or 2500 mg/m^3 in one trial, and to concentrations of 0, 25, 75, or 200 mg/m^3 in the other. No exposure related adverse effects were noted for any of the measured parameters up to the dose of 600 mg/m^3. At 2500 mg/m^3, significant decreases in body weight gain, food consumption, blood urea nitrogen (BUN) and absolute liver weight were recorded in both sexes, as well as significant increases in blood glucose and adrenal and testicular weights in the males. Degenerative changes in the nasal olfactory epithelium, and hyperplasia of the nasal respiratory epithelium and goblet cells were noted at and above the 600 mg/m^3 exposure level.

- Rats exposed to isobutyl lactate at concentrations of 0, 100, 200, 400 or 800 mg/m^3 experienced no exposure-related clinical signs or changes in body/organ weights, feed consumption, hematology or serology. Exposure-related hyperplastic changes of the nasal respiratory epithelium and goblet cells were noted in most rats at the 400 mg/m^3 level, and in all rats at the 800 mg/m^3 level, and "slight derangement" of the nasal olfactory epithelium was also noted in most of the rats in the high dose group.

- With respect to *n*-butyl lactate, rats exposed at concentrations of 0, 75, 200 or 600 mg/m^3 experienced no exposure-related mortality, clinical signs, or body or organ weight changes at any concentration. Very slight to slight focal hyperplasia of nasal transitional epithelium and of nasal respiratory epithelial goblet cells was noted at 600 mg/m^3.

Overall, then the No Observed Adverse Effect Level (NOAEL) for these three studies was 200 mg/m^3, and the critical effect was clearly nasal irritation. Clary *et al.* felt that the similarity of effects and the results of *in vitro* hydrolysis kinetic parameters implicated lactic acid as the most likely cause of the lactate toxicity. With respect to purely systemic, rather than local, toxicity, the NOAEL of these esters was determined to be 600 mg/m^3.

- The study of the ethylhexyl ester exposed rats to concentrations of 0, 75, 200, 600 or 1800 mg/m^3. Histopathological changes in the respiratory tract were found in all dose groups. The 75 mg/m^3 group exhibited hyperplastic changes that were confined to the transitional and respiratory epithelium of the nasal cavity, but in all other dose groups, inflammatory and degenerative changes were noted throughout the respiratory tract (nasal epithelial hyper- and metaplasia, laryngeal and tracheal epithelial hyperplasia and squamous metaplasia, pulmonary septal fibrosis). At the 1800 mg/m^3 dose, decreased food intake and growth retardation were noted, making the NOAEL for systemic toxicity 600 mg/m^3.

- In a follow-up study of the same compound, six male rats were exposed nose-only 6 hours/day, 5 days/week for 4 weeks to both aerosols and vapors (separately) at a concentration of 75 mg/m^3. No changes were recorded for body or organ weight(s), and no clinical signs were noted. Histopathologic changes to the nasal epithelium after exposure to the aerosol were similar to those recorded in the previous study. The nasal response was judged to be similar but less intense in the vapor exposed animals, and the investigators estimated the NOAEL for 2-ethylhexyl lactate at 50 mg/m^3.

Clary *et al.* do not offer an explanation for the mechanism of toxicity of the ethylhexyl ester, but because they treat it separately from the three lower molecular weight esters, they appear to imply that its mechanism, unlike the others, is not *via* hydrolysis to lactic acid. Alternatively, the implication may be that this same hydrolysis step yields an alcohol which is substantially more irritating than the lower molecular weight alcohols, and consequently, either interacts with lactic acid or is sufficiently more irritating than lactic acid to be the actual agent driving the observed nasal toxicity of the ethylhexyl lactate. Whether the obviously higher respiratory toxicity of the ethylhexyl lactate has relevance to the development of a screening level for lactic acid, thus, remains open to question.

ACGIH (1991), while not listing a TLV for lactic acid, has derived one for *n*-butyl lactate (138-22-7). That TLV is set to 30 mg/m^3, based on avoidance of upper respiratory irritation and headache. If one accepts the contention of Clary *et al.* that the lactate esters are likely to dissociate into lactic acid and an alcohol on contact with mucous membranes, an occupational exposure limit (OEL) for *n*-butyl lactate might provide, in conjunction with toxicity data for *n*-butanol, some insight into the inhalation toxicity of lactic acid. Unfortunately, the TLV for *n*-butyl lactate is rather poorly documented, noting two separate unpublished communications whose findings conflict with each other concerning the air concentration that results in adverse effects in the exposed. These equivocal results render the TLV inadequate for the derivation of a screening level.

Derivation of the ITSL: In developing a screening level for lactic acid, the fundamental issue concerns whether one should use acute oral toxicity data specific for lactic acid (and assume that toxicity *via* the oral route is representative of inhalation toxicity), or use inhalation data from related compounds (and assume that their toxicity is minimally affected by their structural differences from lactic acid). Either approach is susceptible to reasoned criticism. Lack of access to long-term ingestion studies specific to lactic acid is also a complicating factor.

Consider first the use of oral data specific for lactic acid. As noted previously, lactic acid is a normal metabolite. Thus, its systemic toxicity largely relates to its accumulation in sufficiently high concentrations to cause gross metabolic derangement (*e.g.*, acidosis and its consequent effects). As noted, we were unable to examine three ingestion studies cited by Clary *et al.*, but apparently none showed evidence of adverse systemic effects from lactic acid ingestion even with exposures of up to 5% (50 g/kg or 50,000 ppm) for a two-year duration. Conversely, acute studies place the oral LD_{50} at 1.8 to 4.8 g/kg, depending on the species of the test animal. These findings, taken at face value, suggest that as long as exposure occurs gradually over a period of time, ingestion of fairly massive doses can occur with minimal systemic toxicity, and that lactic acid exposure by ingestion may be more toxic acutely than chronically. Given this, doubts could be raised as to how relevant bolus gavage administration of a high dose of lactic acid is to health risk assessment for long-term exposures. However, if one is willing to discount these potential extrapolation concerns, the LD_{50} reported for guinea pigs (1810 mg/kg) could be used here to calculate the ITSL. The figure for toxicity in guinea pigs would be used rather than those from other test animals since it appears to have been the most sensitive species to the effects of lactic acid. Per R232(1)(h) of part 55, Act 451, as amended:

$$\text{ITSL} = \frac{1}{500} \times \frac{1}{40} \times \frac{1}{100} \times \frac{LD_{50}\ (\text{mg/kg}) \times W_A}{0.167 \times I_A}$$

where:

W_A = Body weight of a strain- and sex-unspecified guinea pig (midpoint of the range noted by Smyth *et al.* (1941))

I_A = Daily inhalation rate of a strain- and sex-unspecified guinea pig (as calculated from allometric equations[2] from MDEQ, 1996 and EPA, 1988)

So,

$$\textbf{ITSL} = (0.002) \times (0.025) \times (0.01) \times \frac{(1810\ \text{mg/kg}) \times (0.275\ \text{kg})}{(0.167) \times 0.226\ \text{m}^3/\text{day}}$$

$$= (0.0000005) \times \frac{498\ \text{mg/kg}}{0.038\ \text{m}^3/\text{day}}$$

$$= (0.0000005) \times (13{,}105\ \text{mg/m}^3)$$

[2]Allometric relationship for estimating inhalation rate (m^3/day) for guinea pigs:
Inhalation rate (I)= $0.44(\text{weight}^{0.5156}) = 0.44((.275\ \text{kg})^{0.5156}) = 0.44(0.5139) = 0.226\ \text{m}^3/\text{day}$

$$= (0.0066\ \text{mg/m}^3) \times \frac{1000\ \mu\text{g}}{1\text{mg}}$$

$$= 6.6\ \mu\text{g/m}^3 \approx \mathbf{7\ \mu g/m^3}$$

Per 232(2)(c), an annual averaging time would apply.

It seems worthwhile to compare this potential value for the ITSL to those that might be obtained by using the previously discussed inhalation data for the lactate esters. Considering first the acute 4 hr LC_{50} concentrations for low molecular weight lactate esters, the lowest LC_{50} was that of the isoamyl ester, reported by Clary *et al.* (1998) to be >4310 mg/m^3. Per R232(1)(f) of part 55, Act 451, as amended:

$$\text{ITSL} = \frac{LC_{50}}{(500)(100)}$$

$$= \frac{4310\ \text{mg/m}^3}{(50{,}000)}$$

$$= 0.086\ \text{mg/m}^3 \times \frac{1000\ \mu\text{g}}{1\text{mg}}$$

$$= 86\ \mu\text{g/m}^3$$

Adjusting this value to account for the differences in molecular weight between isoamyl lactate and lactic acid:

$$\frac{\text{Molecular Weight of lactic acid}}{\text{Molecular Weight of isoamyl lactate}} = \frac{\text{ITSL for lactic acid}}{\text{ITSL for isoamyl lactate}}$$

$$\frac{90.09}{160.24} = \frac{\text{ITSL for lactic acid}}{86\ \mu\text{g/m}^3}$$

$$7747.74\ \mu\text{g/m}^3 = 160.24 \times \text{ITSL for lactic acid}$$

$$7747.74\ \mu\text{g/m}^3 \div 160.24 = \text{ITSL for lactic acid}$$

$$\therefore\ \textbf{ITSL for lactic acid} = 48.35\ \mu\text{g/m}^3 \approx \mathbf{48\ \mu g/m^3}$$

And per 232(2)(c), an annual averaging time would apply. Thus, an ITSL based on acute inhalation data would be approximately seven times higher than one based on acute oral data.

As a final comparison, one could derive a screening level for lactic acid based upon the subacute inhalation studies of lactate esters reported by Clary *et al.* (1998). Studies of the ethyl, *n*-butyl and isobutyl lactate esters all registered a NOAEL of 200 mg/m^3, with nasal irritation as a critical effect. Exposures to the 2-ethylhexyl ester in both vapor and aerosol forms resulted in a Lowest Observed Adverse Effect Level (LOAEL) at the lowest dose tested, 75 mg/m^3. Though a NOAEL for the vapor was estimated to be 50 mg/m^3, no threshold for toxicity was identified experimentally. As with the other esters, the critical effect was nasal irritation. Per R232(1)(d),

$$\text{ITSL} = \frac{\text{NOAEL}}{(35)(100)} \times \frac{\text{hours exposed/day}}{24\ \text{hours/day}} \quad \text{(for the ethyl, } n\text{-butyl and isobutyl esters)}$$

Or

$$\text{ITSL} = \frac{\text{LOAEL}}{(35)(100)(\text{UF})} \times \frac{\text{hours exposed/day}}{24\ \text{hours/day}} \quad \text{(for the 2-ethylhexyl ester)}$$

Where:

UF is an uncertainty factor valued from 1 to 10, determined on a case-by-case basis, considering the type and severity of the adverse effect. In this case, the factor will be assigned a value of 3 (half an order of magnitude on a logarithmic scale)[3].

Substituting:

$$\textbf{ITSL} = \frac{200\ \text{mg/m}^3}{(35)(100)} \times \frac{6\ \text{hrs/day}}{24\ \text{hours/day}} = (0.057)(0.25)$$

$$= 0.0014\ \text{mg/m}^3 \times \frac{1000\ \mu\text{g}}{1\ \text{mg}}$$

[3]Although it is of concern that no threshold for nasal toxicity was identified in the studies of the ethyl hexyl ester, nonetheless, the hyperplastic nasal changes that were noted in the combination vapor/aerosol study were focal and slight. This suggests that Clary's contention that "the no adverse effect level of 2-ethylhexyl lactate was estimated to be only slightly lower than 75 mg/m^3" may not be unreasonable, and thus that these nasal effects, though adverse, should be considered minimal, and do not warrant application of the full tenfold uncertainty factor.

$$= 14.29 \approx \mathbf{14\ \mu g/m^3}$$

Or

$$\mathbf{ITSL} = \frac{75\ mg/m^3}{(35)(100)(3)} \times \frac{6\ hrs/day}{24\ hours/day} = (0.0071)(0.25)$$

$$= 0.0017\ mg/m^3 \times \frac{1000\ \mu g}{1\ mg}$$

$$= 1.78 \approx \mathbf{2\ \mu g/m^3}$$

Adjusting these values to account for the differences in molecular weight between ethyl lactate/2-ethylhexyl lactate and lactic acid:

$$\frac{\text{Molecular Weight of lactic acid}}{\text{Molecular Weight of ethyl lactate}} = \frac{\text{ITSL for lactic acid}}{\text{ITSL for ethyl lactate}}$$

$$\frac{90.09}{118.15} = \frac{\text{ITSL for lactic acid}}{14\ \mu g/m^3}$$

$$1261.26\ \mu g/m^3 = 118.15 \times \text{ITSL for lactic acid}$$

$$1261.26\ \mu g/m^3 \div 118.15 = \text{ITSL for lactic acid}$$

$\therefore$ **ITSL for lactic acid** (based on ethyl lactate) = $10.68\ \mu g/m^3 \approx \mathbf{11\ \mu g/m^3}$

Or

$$\frac{\text{Molecular Weight of lactic acid}}{\text{Molecular Weight of 2-ethylhexyl lactate}} = \frac{\text{ITSL for lactic acid}}{\text{ITSL for 2-ethylhexyl lactate}}$$

$$\frac{90.09}{202.3} = \frac{\text{ITSL for lactic acid}}{2\ \mu g/m^3}$$

$$180.18\ \mu g/m^3 = 202.3 \times \text{ITSL for lactic acid}$$

$$180.18\ \mu g/m^3 \div 202.3 = \text{ITSL for lactic acid}$$

$\therefore$ **ITSL for lactic acid** (based on the 2-ethylhexyl ester) = 0.89 $\mu g/m^3$
$\approx$ **0.9 $\mu g/m^3$**

And per 232(2)(c), an annual averaging time would apply. *Via* analogous calculations, an ITSL for lactic acid based on either the *n*-butyl or isobutyl lactate esters would be 9 $\mu g/m^3$. So, ITSLs based on subacute inhalation data for lactate esters would span an ITSL based on acute oral data, but would differ from it by ≤ 7 $\mu g/m^3$ irrespective of the ester which one chose to drive the ITSL derivation.

The fundamental conclusion to be drawn from all these calculations, then, is that whether one considers the use of acute oral toxicity data specific for lactic acid, or inhalation data from related compounds, to be more appropriate, the ITSLs that result all fall within a very similar range. Given this fact, and the fact that the Air Toxics rules more clearly provide for the use of acute oral data on a specific compound for ITSL derivation than the use of inhalation data for related compounds, the **ITSL for lactic acid will be based on the guinea pig LD_{50} of Smyth *et al.* (1941), and set at 7 $\mu g/m^3$, annual averaging .**

It should be noted in closing that as long-term animal inhalation studies or human epidemiological studies of sufficient quality for derivation of an ITSL become available, this screening level derivation for lactic acid should be reexamined and revised, as deemed appropriate.

References

ACGIH (1991). *n*-Butyl Lactate (138-22-7). *In*: Documentation of Threshold Limit Values and Biological Exposure Indices, American Conference of Governmental Industrial Hygienists, Cincinnati, OH, p. 182.

Anonymous (1998). Final report on the safety assessment of glycolic acid, ammonium, calcium, potassium, and sodium glycolates, methyl, ethyl, propyl, and butyl glycolates, and lactic acid, ammonium, calcium, potassium, sodium, and TEA-lactates, methyl, ethyl, isopropyl, and butyl lactates, and lauryl myristyl, and cetyl lactates. *Int J Toxicol* **17**(Suppl. 1):1-241.

Clary JJ, Feron VJ, van Velthuijsen JA (1998). Safety assessment of lactate esters. *Regul Toxicol Pharmacol* **27**:88-97.

Cosmetic Ingredient Review (1997). Safety Assessment of Glycol Acid, Ammonium, Calcium, Potassium and Sodium Glycolate and Lactic Acid, Ammonium, Calcium,

Potassium, Sodium and TEA-Lactate, Methyl, Ethyl, Isopropyl, and Butyl Lactate and Laural, Myristyl and Cetyl Lactate. June 6, 1997.

EPA (1988). Recommendations For and Documentation of Biological Values For Use in Risk Assessment. Cincinnati, OH: Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency. Document # PB88-179874, EPA Report # EPA/600/6-87/008, 200+ pp. (2/1988).

Farm Chemicals Handbook (1991). Willoughby, OH: Meister Publishing, p. C252.

Hawley GG (1981). The Condensed Chemical Dictionary. Tenth Ed. Van Nostrand Reinhold Company, New York, p. 347.

MDEQ (1996). Default animal data for risk assessment (as based on U.S. EPA, 1988, Recommendations for and documentation of biological values for use in risk assessment, EPA Document # PB 88-179874).

RTECS (1999). Lactic acid (50-21-5). *In*: Registry of Toxic Effects and Chemical Substances Database. National Institute for Occupational Safety and Health, Public Health Service, Centers for Disease Control, U.S. Department of Health and Human Services, and Canadian Centre for Occupational Safety and Health.

Smyth HF, Seaton J, Fisher L (1941). The single dose toxicity of some glycols and derivatives. *J Indus Hyg Toxicol* **23**:259-268.

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