MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

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INTEROFFICE COMMUNICATION

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TO: File for Ethyl Hydroxyethyl Cellulose (CAS # 9004-58-4)

FROM: Keisha Williams, Air Quality Division

DATE: January 22, 2019

SUBJECT: Screening level update for ethyl hydroxyethyl cellulose

The AQD Toxics Unit has determined that it is appropriate to use the approach described in footnote #26 of the air toxics screening level list, where a toxic air contaminant (TAC) is regulated under the national ambient air quality standards (NAAQS) for particulate matter (PM).

The AQD Toxics Unit conducted a thorough review of the toxicological literature for ethyl hydroxyethyl cellulose in 1997 (see attached memo dated July 9, 1997). Through that assessment, an initial threshold screening level (ITSL) was derived. This ITSL was based on an occupational exposure limit for a similar chemical, cellulose, which is considered a nuisance particulate with little to no chemical-specific toxicity. This TAC is reasonably anticipated to appear in regulated air emissions as PM. So, to ensure health protection, this TAC will be regulated through the current, applicable PM NAAQS along with the combined ambient impact of all particulate emissions from a process.

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

July 9, 1997

TO: File for Ethyl hydroxyethyl cellulose [EHEC] (CAS # 9004-58-4)

FROM: Dan O'Brien, Toxics Unit, Air Quality Division

SUBJECT: Initial Threshold Screening Level (ITSL) for EHEC

The initial threshold screening level for EHEC is 50 µg/m^3 based on an 8 hour averaging time.

The following references or databases were searched to identify data to determine the ITSL: AQD chemical files, IRIS, HEAST, ACGIH TLV Booklet, NIOSH Pocket Guide to Chemical Hazards, RTECS, NTP Management Status Report, EPB Library, IARC Monographs, CAS On-line and NLM/Toxline (1967-May 22, 1997), Handbook of Environmental Data on Organic Chemicals, Patty's Industrial Hygiene and Toxicology, Merck Index and the Condensed Chemical Dictionary.

EHEC is classified as a cellulose ether, and is a hygroscopic white or slightly yellowish/grayish granular odorless solid (Joint FAQ/WHO Expert Committee on Food Additives [JECFA], 1992; Hawley, 1983). It swells when in contact with water, producing a clear to opalescent, viscous, colloidal solution. It is used as a stabilizer, thickening agent, binder, in protective coatings, as a film former in inks, and in various kinds of solvent systems. Water soluble cellulose ethers (of which EHEC is one) are also known as cellulose gums. Other cellulose gums have found application in adhesives, cement and plaster formulations, agricultural products, pharmaceuticals, cosmetics and as a protective coating and glaze for food items (Harris and Sarvadi, 1994). EHEC has been approved as a food additive by the World Health Organization (WHO), which has published specifications for identification and purity testing (JECFA, 1992).

Pharmacological/toxicological literature specific to EHEC is extremely limited. Two references (Wang et al. 1995a,b) were located in which the compound was given orally or intravenously to rats as part of the development of an animal model for acute liver failure in humans. Following subtotal (70-90's) hepatectomy, EHEC reduced bacterial migration through the gut wall and subsequent sepsis in exposed rats. Two other references (Pereswetoff-Morath et al., 1996; Pereswetoff Morath and Edman, 1996) investigated the potential adverse effects of use of EHEC as a nasal drug delivery system. In the former, integrity of nasal mucosa and ciliary beat frequency were studied both in vitro and in rats. EHEC caused "irreversible ciliostasis", which was attributed to the "hypoosmotic nature of the gel". In addition, modest goblet cell hyperplasia was seen in the mucosa of the anterior nasal cavity, which was also considered to be due to "prolonged hypoosmotic conditions" at the site of EHEC deposition. In spite of this finding, the authors concluded that EHEC "can be considered as [a] relatively safe vehicle for nasal administration of drugs". In the latter report, intranasal dosing of rats with equine myoglobin in EHEC generated neither specific IgA nor IgG antibodies in plasma or in nasal washings, and the amount of non-specific immunoglobulins generated did not differ from controls. Intramuscular dosing of the rats with

Freund's adjuvant on day 26 after intranasal dosing with EHEC produced a plasma IgG response similar to controls. It was concluded that EHEC did not potentiate the immunogenicity of heterogeneous proteins. Thus, the available data specific to EHEC suggest portal of entry effects (ciliostasis, goblet cell hyperplasia) which may make extrapolation of oral toxicity data to inhalation routes of exposure inappropriate. However, they also suggest these effects may be relatively modest, local to the site of deposition and due to the physical characteristics of the agent (i.e., the fact that it is a gel) rather than to any inherent biological toxicity.

Most of the systemic toxicity studies available for the cellulose gums as a group have involved oral exposures, and by and large, the gums have been found to be of "low toxicity" (JECFA, 1990) or "essentially innocuous" (Harris and Sarvadi, 1994). Of these, work on hydroxyethyl cellulose [HEC, 9004-62-0] (the gum most structurally similar to EHEC) in rats has shown no systemic toxicity even at high doses. When administered to rats in single oral doses as high as 23 g/kg (50% in corn oil), no toxic effects were observed. Rats maintained for a two year lifetime on diets containing ≤5% HEC showed no toxic effects (Harris and Sarvadi, 1994). In the few situations where toxic effects (hematologic and biochemical changes, renal failure, hypertension, arterial lesions) have been reported, exposure has been via intraperitoneal or intravenous injections (Harris and Sarvadi, 1994). Given the propensity of the cellulose gums to form viscous colloidal solutions in water, reports of such effects with injection exposures are hardly surprising, and of little or no relevance to derivation of a screening level.

JECFA (1990) reports a "substantial body of human data" on the laxative effects of modified celluloses (cellulose gums), which are seen in some subjects at levels as low as 5 g per person per day. At higher doses diarrhea was reported in some subjects, but in others constipation developed. The amounts ingested in studies in humans did not exceed 30 g per person per day, which has been recommended by the National Research Council as the upper safe level of dietary fiber in general. While these results have limited relevance to inhalation exposures of EHEC to humans, they do point out that even the adverse effects of EHEC are not severe or life threatening under normal circumstances. JECFA decided that the Acceptable Daily Intake (ADI) of ≤25 mg/kg body weight previously established for other modified celluloses (methyl cellulose, methyl ethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose and sodium carboxymethyl cellulose) should also apply to EHEC. They note that a toxicological monograph on EHEC was prepared, but that document was not available for our review.

While no specific data regarding the carcinogenic potential of EHEC were available for review, studies of other cellulose gums note that "no carcinogenic potential is expected in normal use" (Harris and Sarvadi, 1994). In long term/carcinogenicity studies on hydroxypropyl methyl cellulose, methyl cellulose, methyl ethyl cellulose and sodium carboxymethyl cellulose in rats and mice, no evidence of mutagenicity or carcinogenicity was observed (JECFA, 1990). In addition, in reproduction and teratogenicity studies in mice, rats, and rabbits, the consumption of hydroxypropyl cellulose, methyl cellulose, or sodium carboxymethyl cellulose did not interfere with the reproductive process, and no embryotoxic or developmental effects were observed.

With respect to the skin irritation/sensitization potential of EHEC, no specific data were located in our searches. However, Harris and Sarvadi (1994) have noted, in summary, that other cellulose gums have been considered nonirritating and nonsensitizing for several decades, and cite references of a number of negative tests conducted in both animals and humans. A single case report of eczema of the hands in a baker was attributed to carboxymethyl cellulose after a positive closed-patch test (2% in petrolatum).

Given the minimal evidence of systemic toxicity of EHEC and the fact that it is a particulate when not mixed with water, the greatest possibility of toxic effects from inhalation exposures may be portal of entry effects and the non-specific respiratory effects of particulate matter in general. The American Conference of Governmental Industrial Hygienists (ACGIH) has established a Threshold Limit Value (TLV) of 10 mg/m^3 (total dust) for a parent compound of EHEC, cellulose [9004-34-6] (ACGIH, 1991). ACGIH considers technical cellulose to be "biologically nontoxic", and notes that human studies show that oral doses of up to 30 g/day can be tolerated as a bulk-forming laxative. The TLV documentation also reports that "airborne cellulose dust is neither irritating nor toxic". Cellulose is considered a "nuisance" dust "which seems to have little adverse effect on the lung and does not produce significant organic disease or toxic effect when exposures are kept under reasonable control". The National Institute for Occupational Safety and Health (NIOSH) has derived a Recommended Exposure Level (REL) for cellulose as well, 10 mg/m^3 (total dust) and 5 mg/m^3 (respirable particulate). In contrast to ACGIH, NIOSH considers cellulose to be an eye and respiratory irritant (NIOSH, 1994). Although neither organization has published Occupational Exposure Limits (OELs) specifically for EHEC, the available data appear to suggest reasonable concurrence between the toxicological characteristics of cellulose and those of EHEC. It should be noted, however, that the two agents do differ with respect to their solubilities in water, cellulose being insoluble. To the extent that water solubility may affect the toxicity of cellulose and EHEC, it is conceivable that the use of OELs for cellulose to derive the ITSL for EHEC might not be appropriate.

In choosing data for screening level development, preference is generally given to human epidemiologic data or chronic laboratory animal inhalation studies which can be used to derive a Reference Concentration (RfC). Such data were not found in our searches. When adequate data for RfC calculation are not available, next preference is given to oral data for calculation of a Reference Dose (RfD) if available data do not indicate that extrapolation from the oral to the inhalation route of exposure is inappropriate. With respect to EHEC, no chronic oral data are available. Even if they were, at least some evidence exists (Pereswetoff-Morath et al., 1996) to suggest that portal of entry effects may make an oral to inhalation extrapolation unwise. OELs, though not available specifically for EHEC, are available for the parent compound of EHEC (cellulose), and the available literature suggests that, like EHEC, cellulose has little potential for systemic toxicity. Rather, the toxic effects noted following inhalation exposures to cellulose, like EHEC, appear to be of limited severity, local to the site of deposition, and consistent with the non-specific respiratory effects of particulates in general. Consequently, it is considered appropriate here to use the NIOSH REL for cellulose (5 mg/m^3 respirable particulate) as the basis for the ITSL for EHEC. Consistent with R232 (1) Cc), the REL is used in preference to the ACGIH TLV, since it is the lower of the two values.

ITSL Derivation: Per Rule 232(1) (c), part 55, of Act 451:

$$ITSL = OELx\frac{1}{100} = 5\frac{mg}{m^3}\ x\frac{1}{100} = 0.05\frac{mg}{m^3}\ x\frac{1000\ \mu g}{1\ mg} = 50\frac{\mu g}{m^3}$$

where the factor of 1/100 is a safety factor to account for: 1) differences in susceptibility between the healthy, adult worker population as compared to the general population which may include individuals or subpopulations more sensitive to the effects of exposure to EHEC and 2) the difference in exposure duration for the worker population as opposed to the general population. The factor is derived as follows:

$$Safety\ factor = \frac{40\ hours}{168\ hours}x\frac{30\ years}{70\ years}x\frac{1}{10} = \frac{1}{100}$$

The first term adjusts for the difference between a 40 hour work week and the total hours in a week; the second factor adjusts for the difference between an assumed working life of 30 years and an assumed total lifespan of 70 years; and the third factor is a standard tenfold uncertainty factor to extrapolate from the healthy worker to sensitive individuals in the general population.

Per 232 (2) (a), since the screening level is based on an OEL with a time-weighted average (TWA) exposure, an 8 hour averaging time applies to this ITSL.

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cc: Tom Julien, Permit Section