MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

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INTEROFFICE COMMUNICATION

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TO: File for Ethylene thiourea [CAS# 96-45-7]

FROM: Doreen Lehner, Toxics Unit, Air Quality Division

DATE: January 19, 2017

SUBJECT: Ethylene thiourea [CAS#] ITSL change in the averaging time from 24 hours to annual

The current initial threshold screening level (ITSL) for ethylene thiourea is 0.28 µg/m^3 based on an annual averaging time. The ITSL established on 1/6/1995 based on an EPA reference dose (RfD) of 0.00008 mg/kg-day. EPAs RfD was derived from a 24-month rat feeding study by Graham et al. (1975) which revealed an increased incidence of thyroid hyperplasia in all dosed rats. When the screening level was derived in 1995 the averaging time was set at 24 hours. As the basis for the screening level used a 24-month feeding study, the averaging time may appropriately be set at annual. Therefore, the averaging time is being changed from 24 hours to annual at this time.

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MICHIGAN DEPARTMENT OF NATURAL RESOURCES

INTEROFFICE COMMUNICATION

January 6, 1995

TO: File for Ethylene Thiourea (CAS # 96-45-7)

FROM: Dan O'Brien

SUBJECT: Initial Threshold and Initial Risk Screening Levels for Ethylene Thiourea (ETU)

The initial threshold screening level (ITSL) for ethylene thiourea is 0.28 $\mu g/m^3$ based on a 24 hour averaging time. The initial risk screening level (IRSL) for ethylene thiourea is 0.01 $\mu g/m^3$ based on an annual averaging time.

The following references or databases were searched to identify data to determine the ITSL and IRSL: 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 - October 24, 1994), CESARS, Handbook of Environmental Data on Organic Chemicals, Patty's Industrial Hygiene and Toxicology, Merck Index and Condensed Chemical Dictionary.

ETU has been widely used as an accelerator in neoprene rubber production and as a part of a curing system for polyacrylate rubber (NTP, 1992). It is also a major degradation product of the metal salts of ethylenebisdithiocarbamic acid, which have been used extensively as agricultural fungicides. Additionally, it has been used as an intermediate for antioxidants and in the manufacture of synthetic resins.

ETU is known to be both teratogenic (CESARS, 1994; IRIS, 1994; Khera 1987; Stein *et al.*, 1978) and carcinogenic (U.S. EPA, 1988; IARC, 1987; Weisberger *et al.*, 1981; Gak *et al.*, 1976; Graham *et al.*, 1975; Ulland *et al.*, 1972) in animals. Though adequate data demonstrating carcinogenicity in humans is lacking, ETU is anticipated to be carcinogenic in humans as well (NTP, 1992, IARC, 1987; Stein *et al.*, 1978).

The critical target organ for the toxic effects of ETU in adult animals is the thyroid gland. The chemical is a structurally-related analog of anti-thyroid drugs that act by inhibiting synthesis of thyroxine (T_4) (NTP, 1992). As secretion of T_4 decreases, the pituitary responds by increasing secretion of thyroid stimulating hormone (TSH), resulting in hyperplastic thyroid tissue which may progress to a neoplastic state with prolonged exposure. Thyroid hyperplasia does not inevitably lead to development of adenomas and carcinomas, however (IRIS, 1992), and at least one study (Freudenthal, 1977)

has demonstrated a plateau and reversibility of thyroid effects in rats following the withdrawal of ETU from the diet. Liver effects have also been observed. Several fetal tissues are targets of the teratogenic effects of ETU; these include the central nervous system and musculoskeletal system. ETU has been tested extensively for genotoxicity in a variety of *in vitro* and *in vivo* systems with the results being overwhelmingly negative (NTP, 1992).

ITSL Derivation: While overlap exists between dose ranges, general toxic effects of ETU tend to occur at doses lower than those which lead to teratogenic or carcinogenic outcomes. Gak et al. (1976) noted hypercholesterolemia in both hamsters and rats of both sexes at a dietary level of 5 mg/kg fed for 20 months. Ulland and coworkers (1972) observed increased incidences of hyperplastic goiters in both male and female CD rats exposed to ETU at levels of 175 and 350 ppm in feed for 18 months. An unpublished study reviewed by Rohm and Haas Company and cited by EPA (IRIS, 1994) reported increased incidences of thyroid hyperplasia in CD-1 mice of both sexes exposed to dietary levels of 100 ppm ETU for 90 days, and increased liver weights in females only at the same level of exposure. IRIS also cites two unpublished six month studies in which thyroid follicular cell hyperplasia was noted in rhesus monkeys exposed to 50 and 250 ppm ETU; the histologic changes were mild at the former dose and moderate to severe in the latter. Decreased serum T_4 concentrations were also noted in these studies at the 250 ppm dose level.

In a chronic (2 year) feeding study by NTP (Chhabra et al., 1992; NTP, 1992), F344/N rats and B6C3F1 mice of both sexes showed dose-related increases in the incidence and severity of thyroid follicular cell hyperplasia in response to ETU exposure. Rats exposed only as adults at 83 and 250 ppm also exhibited decreased T_4 and increased TSH concentrations in serum; perinatal-only exposure resulted in increased thyroid hyperplasia only in the high dose (90 ppm) group. The lowest dietary level tested in the adult-only exposures (83 ppm) was considered the LOAEL for the rats. In the mice, exposure to 330 or 1000 ppm resulted in dose-related increases of thyroid follicular cell hyperplasia with associated increases in TSH levels. The authors considered 1000 ppm to be the LOAEL for mice.

With respect to exposure levels leading to teratogenic effects, IRIS (1994) cites the gavage studies of Khera in mice, rats and rabbits which show LOAELs for developmental toxicity of around 5 mg/kg/day. In a review of teratogenicity studies, Khera (1987) notes the occurrence of hydrocephalus in rats at maternal doses of 30 mg/kg and above, with developmental anomalies occurring in other organ systems (alimentary, musculoskeletal, urogenital) at exposure levels of 80 to 480 mg/kg. A review of CESARS (1994) citations shows various studies reporting teratogenic effects following oral exposure at doses ranging from 10 mg/kg/day to 540 mg/kg/d in a variety of species when administered during organogenesis. The same source lists teratogenic effects at 2.1 and 9.4 mg/kg/day following inhalation exposure. That study (Newell and Dilley, 1978), the only available inhalation study of ETU, is discussed further below. The perinatal exposure portion of the NTP (1992) bioassay found no external gross fetal anomalies or other developmental effects in either mice or rats at any of the studied doses. However, based upon decreased survival of pups and reductions in body weight, NOAELs for

developmental effects of 83 ppm (6.2 mg/kg/day) and 330 ppm (49.5 mg/kg/day) were determined in rats and mice, respectively. It is notable that even the lowest doses observed to cause teratogenic effects are higher than the LOAEL for thyroid hyperplasia. Thus, doses causing developmental effects appear to lie, in general, between those causing general toxic effects and those leading to development of tumors.

EPA lists the inhalation risk assessment for ETU as being under review (IRIS, 1992). The previous RfC (which was based on Newell and Dilley, 1978) was withdrawn, having been considered not verifiable by the EPA RfD/RfC Work Group. The group expressed concern with methodological issues in Newell and Dilley's study, including variability in the exposure chamber ETU concentrations, and the possibility that exposure to light may have degraded the compound. The Group concluded that "this study lacks the necessary experimental detail and toxicological data to provide a firm basis for derivation of an RfC" (U.S. EPA, 1992). This conclusion also calls into question the validity of the LOAELs for teratogenesis derived from Newell and Dilley as listed above. A suitable oral RfD (IRIS, 1994) for ETU does exist, and no data was found to indicate that extrapolation from the oral route to the inhalation route of exposure was inappropriate. So per Rule 232(1)(b) of Act 348, the ITSL is based on the RfD.

The key study used by EPA for derivation of their RfD was that of Graham *et al.* (1975). Groups of 68 Charles River CD-1 rats per sex per group were fed ETU incorporated into their diets at levels of 0, 5, 25, 125, 250 or 500 ppm for a period of 24 months. Assuming a food consumption rate of 5% of body weight per day, these levels provided doses of 0, 0.25, 1.25, 6.25, 12.5 or 25 mg/kg/day. Major studied endpoints were histopathological exams of endocrine organs and other major tissues, organ weights, and thyroidal uptake of ^{131}I. Thyroid hyperplasia was noted in all exposed rats at rates five to ten times higher than the rates in the controls, except for the two highest exposure groups, where the hyperplasia had progressed to neoplasia. In those two highest groups, significant incidences of thyroid carcinomas and adenocarcinomas were observed. The occurrence of thyroid hyperplasia at the 5 ppm exposure level was not considered preneoplastic, however, as significant incidences of thyroid carcinomas were not noted at either 25 or 125 ppm. With respect to body and organ weights, significant decreases in body weights were observed in rats receiving 500 ppm at both 18 and 24 months. Statistically significant decreases in liver-to-body weight ratios were seen in females fed 5 or 25 ppm, and significant increases in thyroid-to-body weight ratios were noted in both sexes exposed to 500 ppm, and in females exposed to 250 ppm. ^{131}I uptake studies did not reveal a significant dose response relationship. The authors concluded that under the conditions of the study, the LOAEL was 5 ppm, based on the critical effect of thyroid hyperplasia.

The LOAEL of 5 ppm was adjusted to a mg/kg/day basis:

LOAEL[adj] = 5 ppm (mg/kg of feed) x 0.05 (assumed rat food consump. per body weight) = 0.25 mg/kg-day

The LOAEL[adj] was divided by an uncertainty factor (UF) of 3000 to obtain the RfD:

$$RfD = \frac{0.25 \text{ mg/kg-day}}{3 \times 10 \times 10 \times 10} = 0.00008 \text{ mg/kg-day}$$

with the UF composed of 10-fold factors for extrapolation from LOAEL to NOAEL, from rats to humans and from the general human population to sensitive human subgroups. The additional 3-fold factor was applied by EPA "since limited developmental toxicological and multi-generation data are available". EPA lists their confidence in the RfD as medium, with medium confidence in both the key study and the database as a whole.

Per Rule 232(1)(b):

$$\textbf{ITSL} = RfD \times \frac{70 \text{ kg}}{20 \text{ m}^3/\text{day}} = 0.00008 \times 3.5 = 0.00028 \text{ mg/m}^3 \times \frac{1000 \ \mu g}{1 \text{ mg}} = \textbf{0.28} \ \mu g/m^3$$

where 70 kg and 20 m^3 are the average body weight and daily inhalation rate of an adult human, respectively. Per Rule 232(2)(b) a **24 hr averaging time** is applied.

Note that while teratogenic effects have been documented as noted above, no data are apparent at this time to indicate that the RfD (or the ITSL derived from it) would not be protective of teratogenic effects.

IRSL Derivation: A carcinogenicity assessment for ETU is currently under review by an EPA work group (IRIS, 1993). As noted above, a number of studies (Chhabra et al., 1992; NTP, 1992, Weisberger *et al.*, 1981; Gak *et al.*, 1976; Graham *et al.*, 1975; Ulland *et al.*, 1972, Innes *et al.*, 1969) have shown unequivocally that ETU is carcinogenic in animals. With the exception of Innes *et al.*'s study (1969) in which thyroid glands were not examined histologically, all of these studies reported increased incidences of thyroid tumors in response to long term ETU exposure. While these studies have observed increased occurrence of a number different neoplastic processes (among them hepatocellular adenomas and carcinomas, pituitary gland [*pars distalis*] adenomas and carcinomas, mononuclear cell leukemia and Zymbal's gland tumors) in mice or rats of one sex or the other, it is notable that thyroid adenomas and carcinoma are the only tumors which have occurred consistently not only across species but sexes as well. Among usable long term studies, the lowest doses of ETU which have led to statistically significant increases in thyroid tumor incidence range from 83 to 350 ppm in feed. The lowest dose, 83 ppm, was identified in the 2 year NTP bioassay (Chhabra et al., 1992; NTP, 1992). This, coupled with the overall quality of the assay and the fact that this is the most recent study, leads to its choice as the key study for the derivation of the risk screening levels.

Per Rule 231(2)(b) of Act 348, unit risk was derived based upon a linearized multistage carcinogenesis model. The model was fitted to incidence data for thyroid, hepatic and pituitary tumors from the NTP study for each sex and species (F344/N rats and $B6C3F_1$ mice). The upper 95% confidence limit was divided by the maximum likelihood estimate of dose at a risk level of 1 in 10^6

per Rule 231(3)(b) to obtain q_1^* cancer potency estimates. Based upon the literature, the male rat appears to be the most sensitive animal tested with respect to ETU-induced thyroid carcinogenesis. This fact was confirmed by the multistage model results, as thyroid adenoma or carcinoma incidence in male

rats yielded the largest cancer potency estimate of the studied groups, q_1^* = 0.07 mg/kg/day. Model fit was acceptable by modified X^2 test.

Interspecies scaling from the rat to humans is accomplished by

$$q_1^*_{human}\ (mg/kg/day)^{-1} = q_1^*_{animal}\ (mg/kg/day)^{-1} \times [70\ kg/W_r\ (kg)]^{1/3}$$

$$= 0.07\ (mg/kg/day)^{-1} \times [70\ kg/0.46\ kg]^{1/3}$$

$$= 0.07\ (mg/kg/day)^{-1} \times 5.34$$

$$= 0.37\ (mg/kg/day)^{-1}$$

where 70 and W_r are the average adult weights of humans and male F344/N rats (from the NTP bioassay) in kilograms, respectively.

Converting $q_1^*_{human}$ based on oral exposure to $q_1^*_{human}$ based on inhalation exposure [231(3)(f)(ii)]:

$$q_1^*_{human}\ (\mu g/m^3)^{-1} = q_1^*_{human}\ (mg/kg/day)^{-1} \times \frac{20\ m^3}{70\ kg} \times \frac{1\ mg}{1000\ \mu g} \times \frac{a}{b}$$

$$= 0.37\ (mg/kg/day)^{-1} \times 0.29\ (m^3/kg)^{-1} \times 0.001 \times 1$$

$$= 0.0001\ (\mu g/m^3)^{-1}$$

where 20 m^3 and 70 kg are the assumed adult human daily inhalation rate and body weight, respectively, and where *a* and *b* are the absorption efficiency by the inhalation and oral routes of exposure, respectively. Here, in absence of data to the contrary, it is assumed *a* = *b*.

Per 231(2)(b):

$$\text{Unit risk} = q_1^* \times 1\ \mu g/m^3 = 0.0001\ (\mu g/m^3)^{-1} \times 1\ \mu g/m^3 = 0.0001$$

Finally, per 231(1):

$$\textbf{IRSL} = \frac{1 \times 10^{-6}}{\text{unit risk}} = \frac{1 \times 10^{-6}}{0.0001} = \textbf{0.01 } \mu g/m^3$$

$$\textbf{SRSL} = \frac{1 \times 10^{-5}}{\text{unit risk}} = \frac{1 \times 10^{-5}}{0.0001} = \textbf{0.1 } \mu g/m^3$$

and per 231(4), an **annual averaging** time applies.

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