

Health- and Vegetation-Based Effect Screening Values for Ethylene

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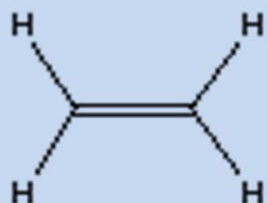
Slides Prepared for the 2014 Symposium on Understanding the Health Risks of Lower Olefins





City of Austin

Ethylene CAS Registry Number: 74-85-1

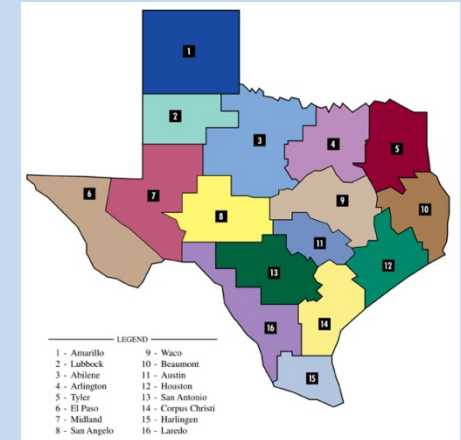


- 19th Century identified as the Illumination gas
- In 1886, Neljubov discovered that ET is the biologically active component of the illumination gas
 - (Chaves, Anna Lucia Soares, 2006)
- According to ACC 2004: Acetene; Elayl; Olefiant Gas; Refrigerant 150; Ethene; UN1038 (refrigerated liquid), UN1962 (compressed liquid), Athyllen [German], Bicarburretted hydrogen; Caswell No. 436; EINECS 200-815-3; EPA Pesticide Chemical Code 041901; Etileno; HSDB 168 (ACC 2004)

TCEQ Process



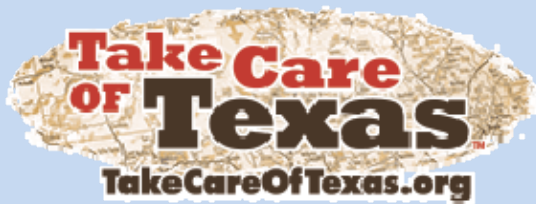
Is it safe?



Background

- ❖ **Goal:** To protect the general population including children and pregnant women from *adverse health effects* and to protect crops , plants, and trees from *adverse vegetation effects* due to potential acute and chronic exposures to Ethylene (ET) in **ambient air**.

Problem Formulation: Human health and Vegetation Effects



TCEQ's Process

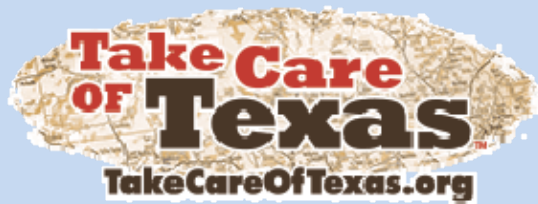


- ❖ Using the Toxicity Factor Guidelines TCEQ developed up to 4 four Screening values called Effect Screening Levels (ESLs) for ET
- ❖ 1) Acute health-based ESL,
- ❖ 2) Acute vegetation-based ESL,
- ❖ 3) Chronic health-based ESL and
- ❖ 4) Chronic vegetation-based ESL.



Definition of ESL

- ❖ Chemical-specific guideline air concentrations set to protect human health and welfare (odor nuisance potential, and adverse vegetation effects)
- ❖ Short-term ESLs are based on data concerning acute health effects, odor nuisance potential, and vegetation effects
- ❖ Long-term ESLs are generally based on data concerning chronic non-carcinogenic and/or carcinogenic health effects and vegetation effects.

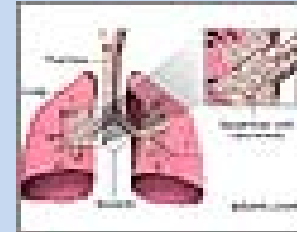


Health Effects Review

- Human Health Effects
 - Acute (e.g. eye irritation)



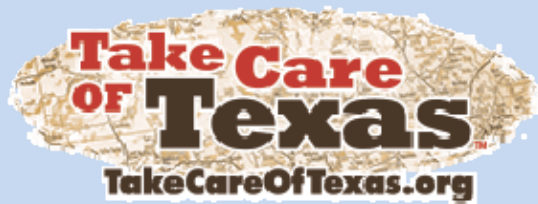
- Chronic (e.g. lung disease, cancer)



- Odor



- Vegetation

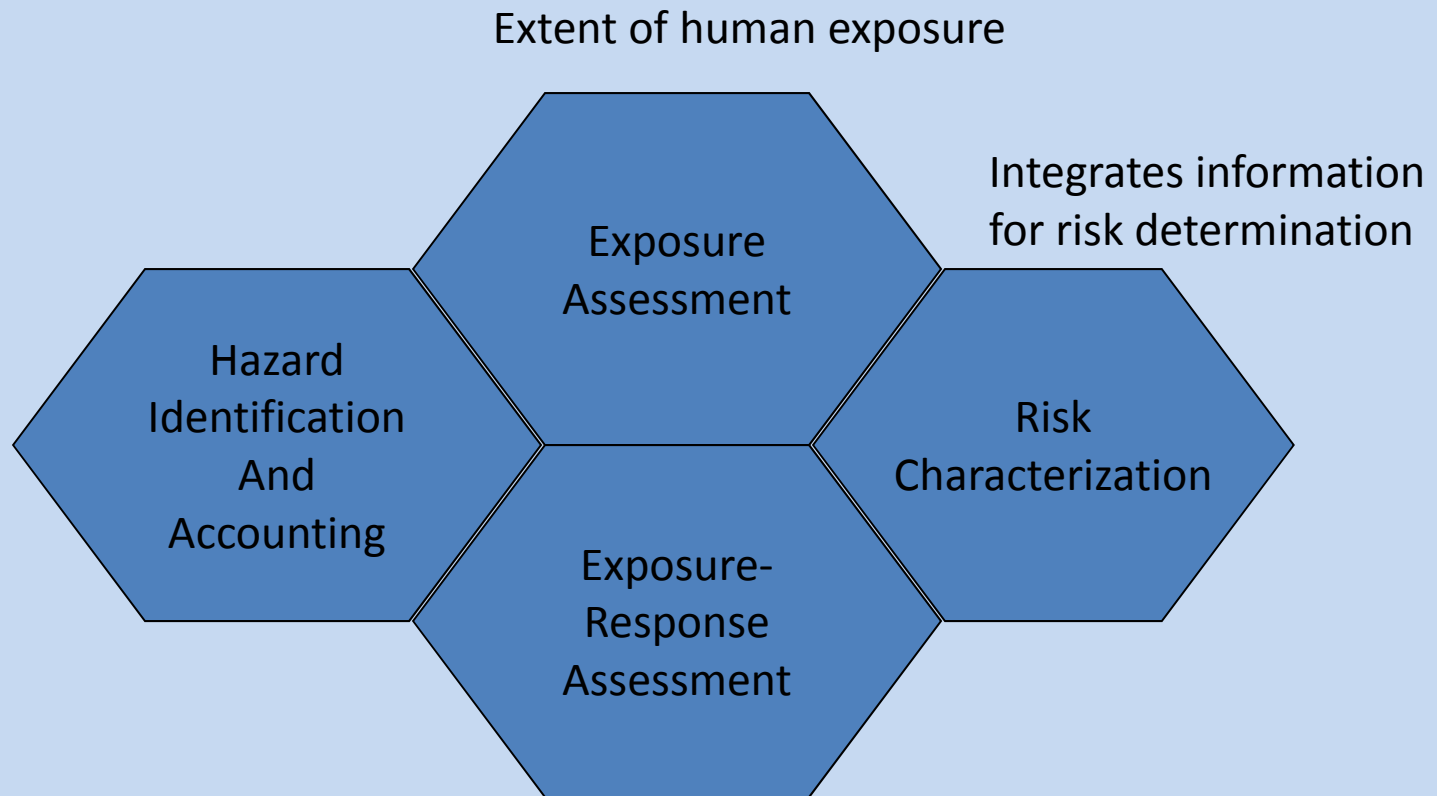


ESLs (cont.)

- ESLs are set to protect sensitive subpopulations such as:
 - ❖ Children
 - ❖ Pregnant women
 - ❖ Elderly
 - ❖ Individuals with pre-existing conditions



Risk Assessment Process



Estimate relationship between magnitude Of exposure and degree/probability of Adverse health effect

Health-based ESLs for ET

- 1) Conduct comprehensive literature review including physical/chemical properties and select key studies;
- 2) Conduct human relevant mode of action (MOA) analysis;
- 3) Choose the appropriate dose metric;
- 4) Determine the POD for key study;
- 5) Conduct appropriate dosimetric modeling and determine the human equivalent POD (POD_{HEC});
- 6) Select critical effect and apply appropriate uncertainty factors (UFs) to determine the reference value (ReV);
- 7) Calculate the appropriate ESL by multiplying the appropriate ReV with 0.3 to account for cumulative effects during the air permit review process.

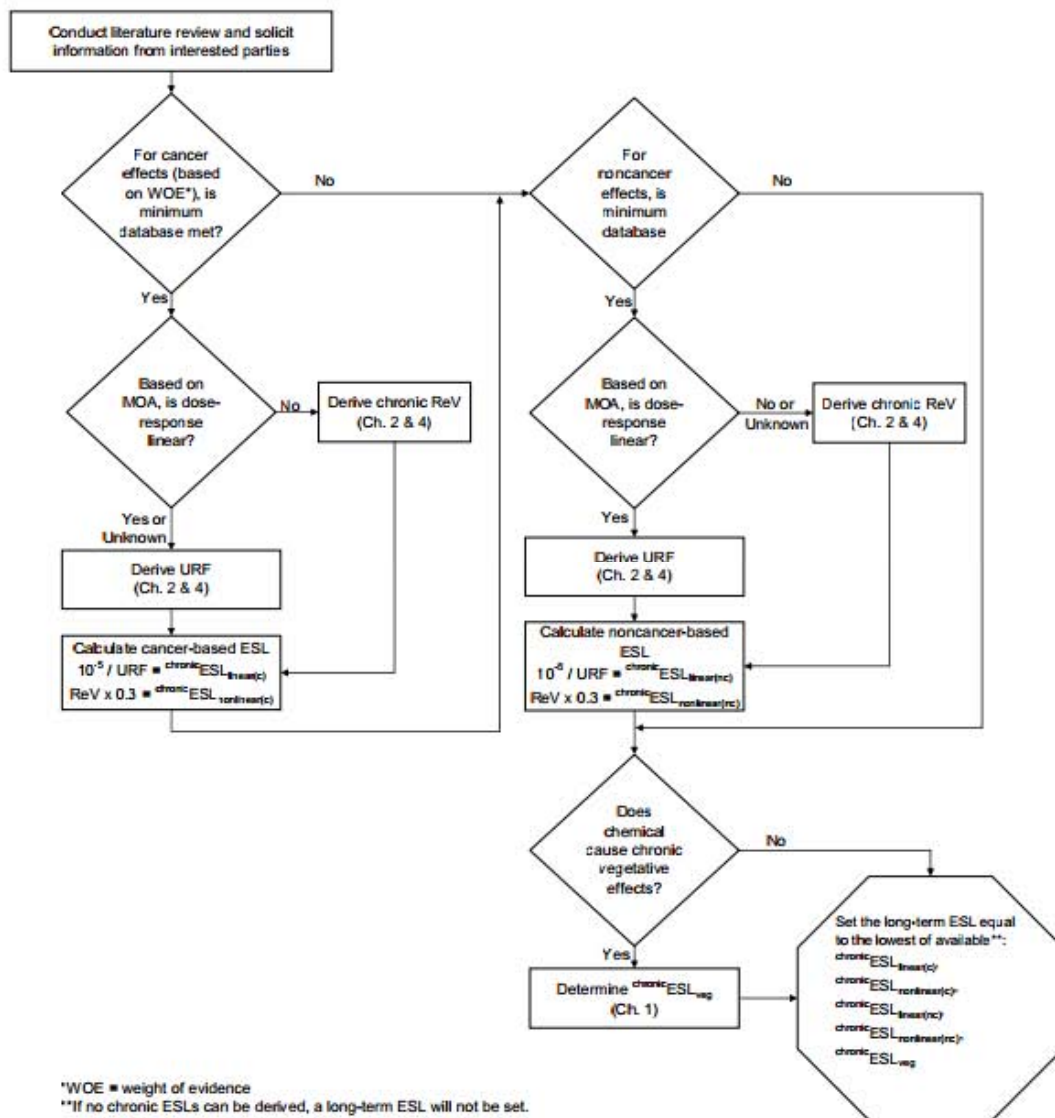


Figure 1-2. Long-term ESL development

Vegetation-based ESLs

- 1) Comprehensive literature review
 - 2) Identify Key Studies
 - 3) Identification of adverse threshold effects or Lowest-Observed-Effect-Level (LOEL) as part of the hazard identification process.
- The magnitude of effects at various exposure concentrations and durations are then reviewed for the dose-response assessment. (TCEQ 2006 and TCEQ 2012).

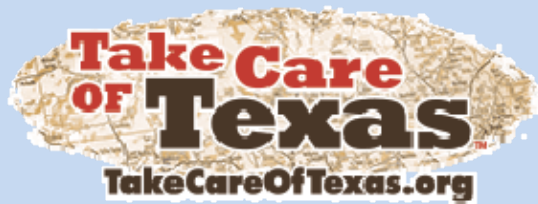


Vegetation-based ESL...

- Hazard identification was based on a few criteria and included:
- Plant species that are native to Texas or known to be grown in the state; and
- Relatively moderate adverse effects such as defoliation, abscission of flower buds, epinasty, failure of seed filling and disproportionate leaf growth, rather than milder effects such as slight dry sepal injury (observed after the sepals are dried).

ESLs

- ESLs used for air permit reviews are 70% lower than ReVs, used as comparison values for air monitoring) (TCEQ 2006, 2012). These procedures were used for both the acute ESLs (using short-term toxicity studies) and chronic ESLs (using long-term toxicity studies).



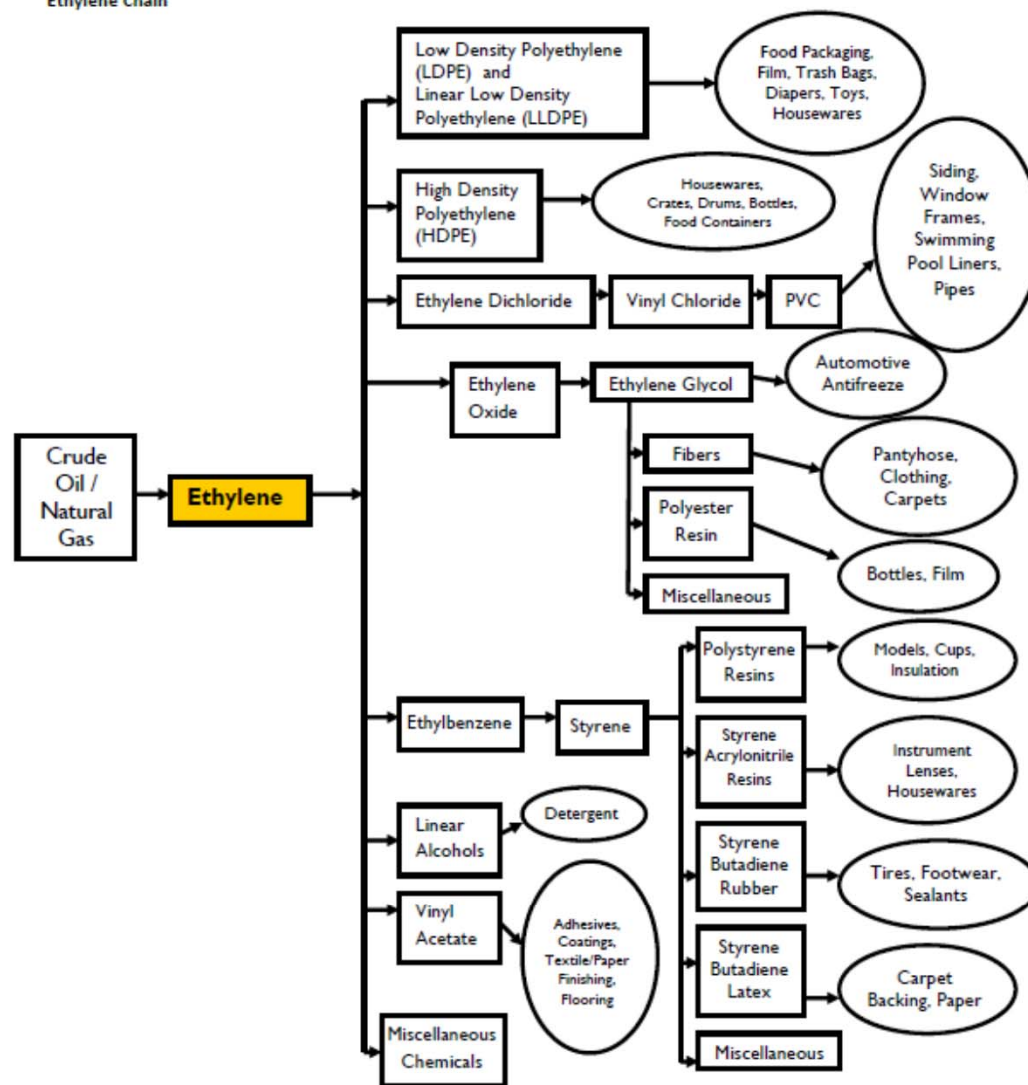
Physical/Chemical Properties

- Highly-flammable volatile gas that is considered to be a fire hazard at sufficiently high concentrations.
- In occupational settings, very high concentrations of ET can lower oxygen concentrations and has been reported to function as an asphyxiant
- It is a colorless gas with a faint sweet odor, is a liquid under pressure, and is slightly soluble in water.
- ET has a low blood-gas partition coefficient and does not accumulate in the body.

Uses and Sources

- Produced both naturally and due to anthropogenic sources
- Largest volume organic chemical produced worldwide
- Produced mainly by the steam-cracking of hydrocarbons.
- Vehicular traffic, forest fires, & active volcanic events due to incomplete combustion fossil fuel biomass
- Was used as an anesthetic in the past. Was discontinued because of its flammable properties & its ability to cause asphyxiation at high concentrations.
- Pesticide
- Regulatory plant Hormone
- Artificial fruit ripening agent
- Produced endogenously in mammals through lipid peroxidation of unsaturated fats, oxidation of free methionine, oxidation of hemin in hemoglobin, and metabolism of intestinal bacteria (Health Canada 2001).

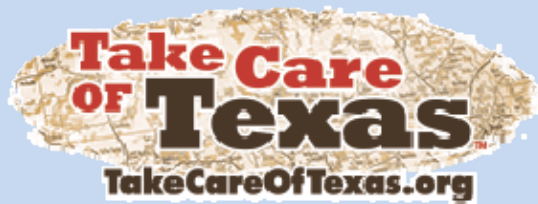
FIGURE 2.6
Ethylene Chain



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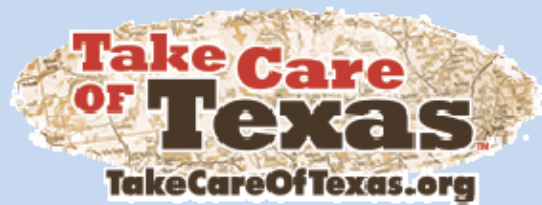
Mode-of-Action (MOA) Analysis

Even though ET has been used as an anesthetic in the past and its continued and prevalent use as an artificial ripening agent and biopesticide indicate it to be non-toxic, there is concern about the potential toxicity of ET because ET is metabolically converted to ethylene oxide (EtO), a suspected human carcinogen, a genotoxicant, and a potent alkylating agent that can form adducts by interacting with cellular macromolecules such as DNA, RNA, and protein (e.g., hemoglobin) (Filser et al.1992, Walker et al.2000, Bolt 1982, Filser et al. 2013).



Genotoxicity, and Carcinogenic Potential

- ET is not mutagenic in *in vitro* studies (Victorin and Stahlberg 1988) & was not mutagenic or genotoxic in *in vivo* studies in rodents (Vergnes and Pritts 1994; Walker et al. 2000).
- No signs of carcinogenicity in rats after 2-year exposure to 3,000 ppm ET (Hamm set al. (1984).
- The International Agency for Research on cancer (IARC) has classified ET as a Group 3 chemical, which indicates that it is a not classified as a human carcinogen (IARC 1994).
- More recently, subchronic exposure of rats to ET up to 10,000 ppm did not result in significant increases in micronucleated erythrocytes in bone marrow (ECHA 2010. REACH Dossier summary IUCLID file for ethylene.).



Pharmacokinetic Information

- Better understand the estimated EtO body.
- Human chamber studies Filser et al. (1992, 2013).
 - A majority (98 %) of ET was exhaled unchanged and only a small amount (~ 2%) of the ET was absorbed and metabolized to EtO in humans.
- The TCEQ considered all the evidence from the different data streams (human chamber, animal exposure, and mechanistic studies) to conclude that ET does not have a mutagenic MOA and that the data are inadequate for an assessment of human carcinogenic potential by the inhalation pathway

Development of a Health-Based Chronic ESL based on Threshold MOA

Chemical Industry Institute of
Toxicology 1980

Hamm et al. 1984



Key Study: Hamm et al. 1984

- Randomly divided 960 Fischer-344 rats into 4 groups of 120 animals/sex & exposed them to 0, 300, 1,000, or 3,000 ppm of ET for 6 (h/d), 5 (d/w) for 106 weeks.
- No reports of any chronic toxicity or oncogenicity
- Comprehensive analysis of various tissues (e.g., kidney and nasal turbinates) indicated no signs of carcinogenic effects.
- Because of the absence of a Lowest-Observed-Adverse-Effect-Level (LOAEL) or any other adverse effects, the TCEQ considered 3,000 ppm as a free-standing NOAEL and is the Point of Departure (POD).



Default Exposure Duration Adjustments

- Adjustment from the discontinuous animal exposure regimen to a continuous exposure regimen with the following equation to determine the adjusted POD (POD_{ADJ})

$$POD_{ADJ} = POD \times (D/24 \text{ h}) \times (F/7 \text{ d})$$

where:

POD_{ADJ} = POD from animal studies adjusted to a continuous exposure scenario

POD = POD from animal studies based on discontinuous exposure scenario

D = Exposure duration, h per day

F = Exposure frequency, days per week

$$\text{The } POD_{ADJ} = 3,000 \text{ ppm} \times (6/24) \times (5/7) = 535.71 \text{ ppm}$$

Default Dosimetry Adjustments

- ET is relatively non-toxic even at high concentrations (up to 3,000 ppm).
- No point of entry (POE) respiratory effects and because the potential critical effect is hepatotoxicity, the TCEQ will consider ET as a Category 3 gas
- Conduct duration exposure adjustments from animals to humans according to USEPA (1994) guidance.
- A default blood : gas partition coefficient of 1
- Human equivalent POD (POD_{HEC}) is calculated using the following equation:

$$POD_{HEC} = POD_{ADJ} \times (H_{b/g})_A / (H_{b/g})_H$$

where,

POD_{ADJ} = Adjusted Point of Departure

$H_{b/g}$ = Ratio of blood:gas partition coefficient

A = Animal

H = Human

The POD_{HEC} based on Hamm et al.(1984) study = **535.71 ppm x 1 = 535.71 ppm**



Critical Effect

- Although no adverse health effects were reported, hepatic damage is presumed to be the critical effect
 - based on the findings that hepatic damage was noted in acute rat studies (Conolly et al. 1978, Guest et al. 1981) when rats were pretreated with polychlorinated biphenyl (PCB) mixture (resulting in enzyme induction), then exposed to ET up to 50,000 ppm.

Adjustments of the POD_{HEC}

- An UF of 3 was applied to account for extrapolation from animals to humans (inter-species variability) (UF_A)
 - Default dosimetric adjustments from animal-to-human exposure were conducted which account for toxicokinetic differences but not toxicodynamic differences.
- An UF of 10 was applied to account for intraspecies variability (UF_H) to account for potential increased sensitivity of children, the elderly, and persons with preexisting disease.
- A UF of 3 was applied to account for database uncertainty factor (UFD) of 3 was applied because of the absence of a multigenerational reproductive study, consistent with U.S. EPA (2002a).

Table 1: Derivation of the Chronic ReV and Chronic ESL

Parameter	Summary
Study	Chronic toxicity and oncogenicity bioassay of inhaled ethylene in Fischer-344 rats
Study population	Fischer-344 rats
Study Quality	Medium
Exposure Method	Inhalation
Critical Effects	Hepatotoxicity
POD (Free-Standing NOAEL)	3,000 ppm
Exposure Duration	6 h/day, 5 days/wk, 2 years
Extrapolation to continuous exposure (POD _{ADJ})	535.71 ppm
POD _{HEC}	535.71 ppm (gas with systemic effects based on default RGDR =1)
Total UFs	100
<i>Interspecies UF</i>	3
<i>Intraspecies UF</i>	10
<i>LOAEL UF</i>	Not Applicable
<i>Subchronic to chronic UF</i>	Not Applicable
<i>Incomplete Database UF (Database Quality)</i>	3 (Medium)
Chronic ReV (HQ = 1)	5,300 ppb
Chronic ESL (HQ = 0.3)	1,600 ppb



Development of a Vegetation-Based ESL

The Alberta Ethylene Research Project (The Alberta Canada Study)

The Alberta Canada Study

Exposure Scenario 2:

- Barley, field peas, and canola were exposed to a range of ET concentrations (10 – 250 ppb) for 14 days
- The investigators reported a 63% reduction in seed yield of barley when barley plants were exposed to 30 ppb for 14 days.
- Based on these result, the TCEQ determined a LOEL of 30 ppb for long-term exposures

Derivation of the Chronic Vegetation - Based ESL

Parameter	Summary
Study	Alberta's Ethylene/Crop Research Project Report III, 2001 (Exposure Scenario 2)
Study population	Barley
Exposure Method	Growth Chambers
Critical Effects	63% reduction in seed yield for barley
POD (Threshold Concentration)	30 ppb
Exposure Duration	14 days
Chronic Vegetation -Based ESL	30 ppb

Conclusions

- Due to concerns of potential human and vegetation effects from exposure to ET from point sources, the TCEQ developed chronic and acute health- and vegetation-based ESLs for ET.
- TCEQ conducted a WOE analysis of the MOA and concluded that the metabolic conversion of ET to EtO does not pose a cancer risk.
- The chronic evaluation resulted in the derivation of a chronic vegetation-based ESL (30 ppb) that was much lower than the chronic health-based ESL (1,600 ppb).

Conclusions...

- Similar to the chronic evaluation, the acute assessment resulted in the derivation of the acute vegetation-based ESL (1200 ppb) that was considerably lower, and therefore, more conservative than the health-based ESL (150,000 ppb) (TCEQ 2008).
- The TCEQ's acute and chronic ESLs for vegetation will protect the general public from both short-term and long-term adverse health and welfare effects respectively.
- The general public includes children, the elderly, pregnant women, and people with pre-existing health conditions.

Short-Term Values	Concentration	Notes
Acute ESL Vegetation-Based	1,200 ppb * Short-Term ESL for Air Permit Reviews	This value is a Lowest-Observed-Effect-Level that is protective of all crop plants including flowering plants
Acute ESL Health-Based (HQ = 0.3)	150,000 ppb	Critical Effect: hepatic damage in male Holtzman rats, based on a free-standing NOAEL
acute ReV (HQ = 1.0)	500,000 ppb	Critical Effect: Same as above
Long-Term Values	Concentration	Notes
Chronic ESL Vegetation-Based	30 ppb * Long-Term ESL for Air Permit Reviews	This value is a threshold concentration that is protective of all crop plants including flowering plants
Chronic ESL Health-Based (HQ = 0.3)	1,600 ppb	Critical Effect: hepatic damage in Fischer 344 rats based on free-standing NOAEL
chronic ReV (HQ = 1.0)	5,300 ppb *	Critical Effect: Same as above
Chronic ESL (Cancer)	---	No evidence of carcinogenic potential

Questions

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Questions

