資料　1

エチレンの使用状況について

エチレンは植物自身が作り出す植物ホルモンとして、その多様な生理活性作用が古くから知られていた。その作用を利用した植物生育調節剤としてエテホン液剤（商品名：エスレル 10 など）が果樹、トマト、キク、カボチャなどの多くの作物を対象として利用されている。エテホン液剤の成分は 2-クロロエチルホスホン酸であり、水溶液として作物に散布される。植物体内において散布後 1～2 日以内にほとんどが分解してエチレン（ガス）を発生し、効果を発現する機作となっている。このため、この農薬の人畜などへの安全性はエチレンではなく、エテホン（2-クロロエチルホスホン酸 ）の安全性が検討され、農薬登録がされている。

コーデックス委員会は、エチレンをバナナとキウイフルーツを追熟させるために有機農産物生産への使用が可能な資材として認定している。それを受けて国内でも同様の措置がとられており（有機農産物の農林規格　**資料６**）、バナナとキウイフルーツの追熟用に一般農業資材として利用されている。一方、エチレンがばれいしょの萌芽抑制に効果があることも広く知られており、既にカナダやイギリスでは農薬として登録、利用されている（**資料７、８**）。

エチレンによる貯蔵ばれいしょの萌芽抑制効果に関する諸外国の情報や研究報告をもとに、国内でもその実用化をめざして北海道馬鈴しょ協議会は、萌芽抑制効果などの確認のための試験を研究機関に委託し、また酪農学園大学を中心として平成 21 年から農林水産省の外部委託研究として「エチレンを用いた加工用馬鈴しょの萌芽抑制による高品質貯蔵技術の開発」が実施されてきた。さらに北海道内の農業協同組合やばれいしょ加工会社は、技術の早急な確立を目指して平成 21 年秋から貯蔵倉庫の一部にエチレンガスを利用した発芽抑制効果の実証試験を開始している。

実証試験に使用されているエチレンガス制御装置を**図１**に示したが、既存の貯蔵倉庫に付置するだけの簡単なものである。ばれいしょの貯蔵倉庫は低温・定温となるように、外気が高温時には冷房機が稼働し、外気が低温時には外気が導入されて、庫内の空気が常時攪拌され定温が保たれている。エチレンの分子量は 28 と空気の平均分子量と近似するため、庫内におけるガスの均一化は容易である。したがって庫内の一カ所からエチレンガスを噴霧し、他の１ないし２カ所で空気をサンプリングしてガス濃度を測定し、噴霧量を調節することにより庫内を一定のエチレン濃度に保つことができる。

実際、萌芽抑制の効果は明瞭で、貯蔵庫内の場所による偏りもなかった。このような実態からばれいしょの萌芽抑制手法の決め手として、今後は貯蔵庫におけるエチレンの利用が進むものと推察される。

これまでに得られた多くの知見から、エチレンは明確な萌芽抑制効果を有し、明らかに人畜および環境などへの有害な作用を及ぼすことがないと考えられる。

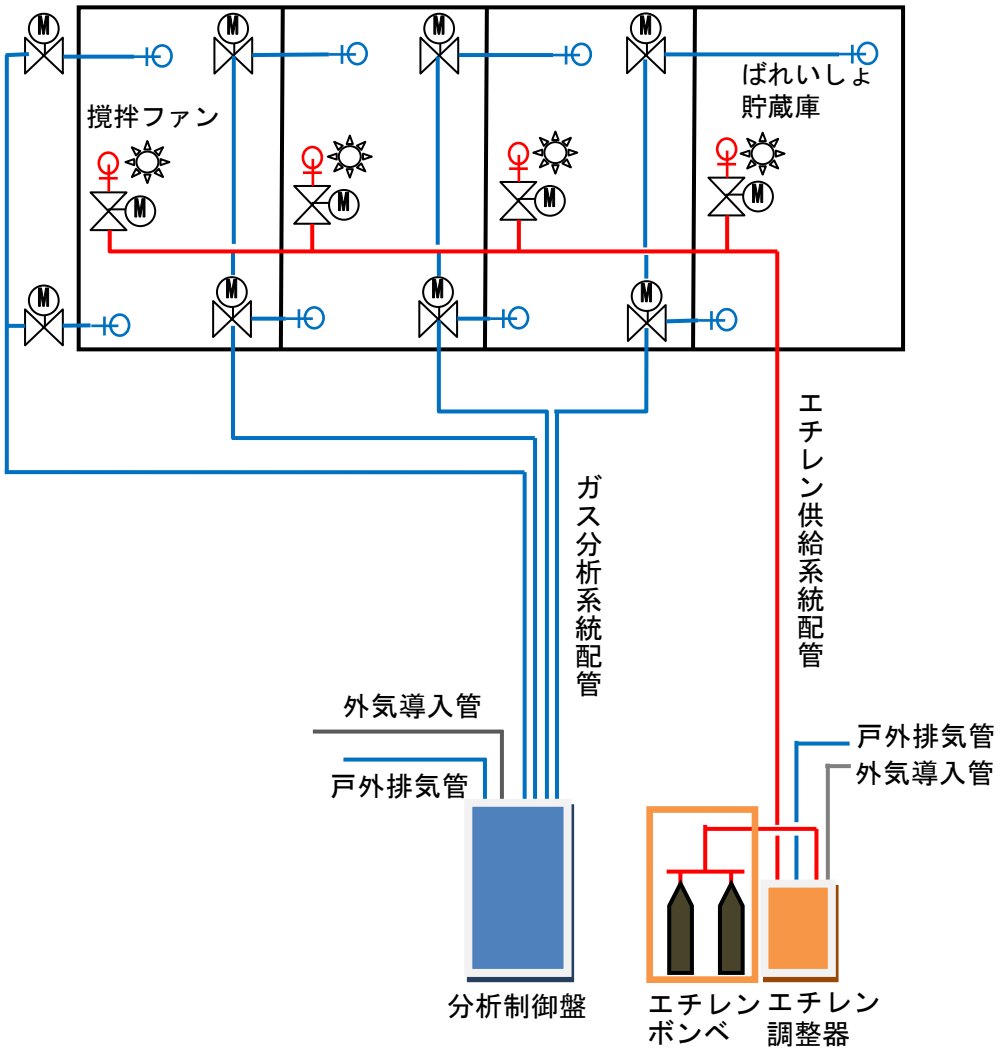


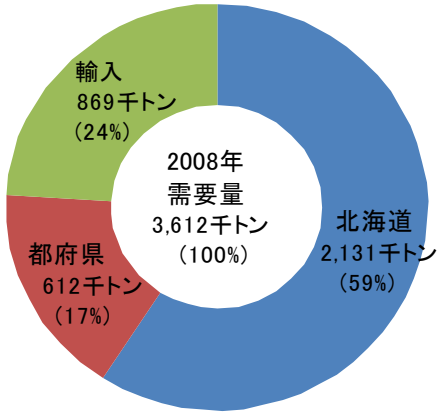
図１．エチレンガス制御装置の概要図（ＪＡ士幌で試用中）

◆エチレンボンベ：100%液化エチレン 10kg
◆エチレン調整器：エチレンを空気で 1:200 に希釈し圧力を調整して供給する。
◆分析制御盤：各貯蔵庫内の空気を吸引してエチレンガス濃度を測定し、設定されたエチレン濃度の下限を下回ると自動的にエチレンガスを供給、上限値で停止し、貯蔵庫内のエチレン濃度を自動制御する。全ての監視および操作は分析制御盤で行う。
◆各貯蔵庫内には鉄製コンテナーに収納されたばれいしょ７トンがおおむね 10 月頃から搬入され、エチレンを使用した発芽抑制貯蔵が開始される。
◆貯蔵庫内の温度は約８℃、湿度は９０%以上に制御され、また二酸化炭素濃度も測定、記録されている。

（参考）

１．ばれいしょ生産の現状

国内におけるばれいしょの年間需要量は約３６０万ｔであり、そのうち国内で生産・供給されるのは２７４万ｔと約８割の自給率である。また北海道では約２１３万ｔが生産され、国産ばれいしょの８割弱、年間需要量の約６割を供給する一大産地となっており、かつ畑作にお



資料：農林水産省 食料需給表（2008）」

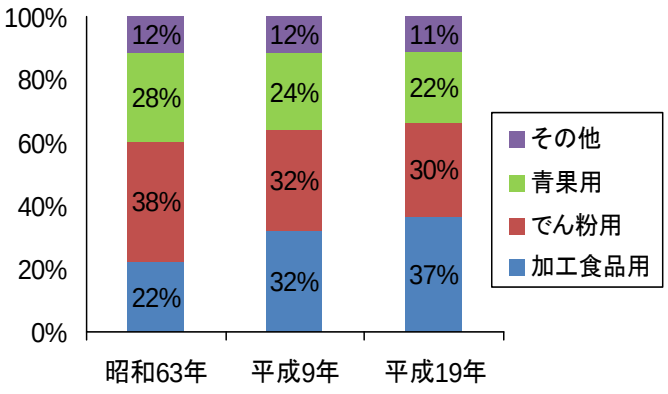
図２．ばれいしょの供給状況

ける重要な基幹作物のひとつである（**図２**，数字はいずれも２００８年）。

ばれいしょは寒冷な気候に適した作物であることから、北海道では春に植え付けし秋に収穫されるが、都府県では秋冬に植え付けし、春～初夏に収穫される。国産ばれいしょは、生いもで流通する「青果（ 生食）用」のほか、ポテトチップス等に加工される「加工食品用」、でん粉に加工され片栗粉や清涼飲料用の異性化糖等に利用される「でん粉原料用」などに供給されている。都府県産のバレイショは主として生食用および加工食品用として収穫後に速やかに消費されるが、年間需要の４分の１の期間に対応しているに過ぎない。一方、北海道産は生産量の約 50%はでん粉原料用として収穫後直ちに加工処理されるが、生食用および加工食品用は収穫後の秋から次年の夏まで貯蔵され、需要に応じて通年で利用されている。

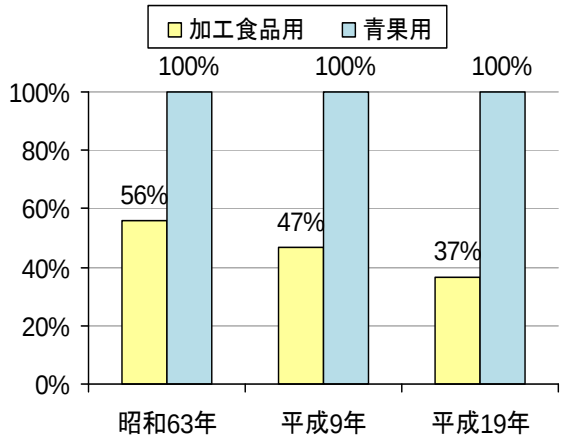
２．ばれいしょ需要の動向

近年、食生活の多様化や外部化等が進む中で、総じて青果（ 生食）用としての需要量が減少し、フライドポテト等の加工食品用が増加する傾向にある。そのため、冷凍品等の形で輸入される加工食品用ばれいしょが増加し、国産のシェアが減少する傾向にある（**図３，図４，図５**）。



資料：農林水産省「いも類の用途別消費実績調査」

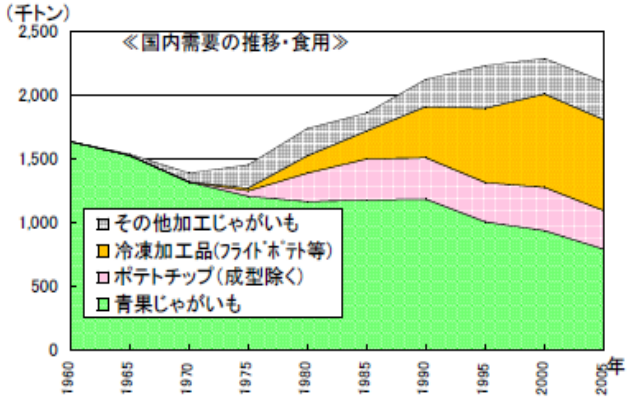
図３．ばれいしょの用途別需要の推移



資料：農林水産省「いも類の用途別消費実績調査」

図４．ばれいしょの加工食品用・青果用の国産シェアの推移

加工食品用ばれいしょ（ 約１３５ 万t ）のうち、ポテトチップス用（ 約 ２９ 万トン）はほぼ全量が国産で供給されており、大半が北海道産となっている。しかしながら後述するように、ばれいしょは低温で長期貯蔵した場合でん粉が糖類に変化して、ポテトチップス加工時に「焦げ」の原因となることから、通常、１０℃ 前後で貯蔵される。しかし、この温度帯で貯蔵した場合には、春先までにいもが休眠から覚め、萌芽による品質低下や減耗が大きな問題となっている。このため、ポテトチップス製造業者においては、新しい道産ばれいしょが収穫されるまでは、原料調達先を九州、関東、東北等の産地に切り換えているが、その品質と供給は必ずしも安定していない。



資料：農林水産省「いも類の用途別消費実績調査」

図５．ばれいしょの用途別需要の推移

３．ばれいしょの貯蔵に関する問題

ばれいしょは水分含量が 75～80％であるため、穀物のように長期貯蔵には元来適していないものの、需要に応えるため低温（5～10℃程度）条件下で長期の保存をおこなっている。しかし品種によって早晩はあるものの、低温下でも数ヶ月を超えると萌芽（発芽）が始まる。萌芽はばれいしょの外観上の商品価値を損なうのみならず、急激なでん粉含量の低下と還元糖の増加をもたらし、販売に適さない品質となる。とりわけ還元糖の増加は油で揚げた際に焦げ色を濃くし、商品価値を低下させると共に、発がん性が疑われているアクリルアミドの含量が高まるため、健康に悪影響をもたらす可能性のあることが懸念されている。

このため、低温条件に加えて萌芽を抑制する方策が従来から講じられてきた。一つは放射線照射（コバルト 60 によるガンマー線照射）による生理活性の失活である。しかし、この方法は設備の保守・維持管理が容易でないこと、さらには消費者から必ずしも理解が得られないことから広く普及するには至っていない。他方、従来から化学合成した植物生育調節剤による萌芽抑制処理が一般には用いられてきた。しかし萌芽抑制剤として使用されてきた「マレイン酸ヒドラジド」は、不純物として含有するヒドラジンの発がん性などから２００２年に販売が中止された。

以上のことから、ばれいしょの長期貯蔵に伴う萌芽抑制に有効な手立ての開発と実用化が、ばれいしょの生産者および実需者にとって緊急かつ重要な問題となっている。

資料　2

化学物質等安全データシート

整理番号　エチレン(可燃性)

作成　平成 5年 3月31日
改訂　平成 8年 5月31日
改訂　平成16年 2月23日
改訂　平成16年12月 1日
改訂　平成20年12月 1日

【製品名】　ダイチレン(液化エチレン)

化学物質等安全データシート

1. 化学物質等及び会社情報

化学物質等の名称:エチレン(可燃性)
製品コード　　:
会　社　名　　:
住　　所　　:
担 当 部 門　　:
連絡先:　Tel　　;FAX;
E-mail;
整 理 番号　　:　エチレン(可燃性)
緊急連絡先　　:

2. 危険有害性の要約

重要危険有害性及び影響　:空気中での爆発限界が低く、又、引火性も極めて高いので爆発火災に対する危険性が大きい。
:高温、高圧下では分解爆発を起こす。
:移送時の流動や噴霧、漏れなどの際に静電気を発生しやすく、わずかな放電火花で爆発する危険性がある。
:高圧ガス容器からガスが噴出し、目に入れば、目の損傷、あるいは失明のおそれがある。
:高濃度のこのガスを吸入すると、麻酔作用があり、また窒息により死亡することがある。
:超低温のため、直接または超低温状態の配管等に接触すると凍傷を起こすことがある。
:超低温容器または貯槽が高温にさらされると、容器内の圧力が異常上昇して破裂のおそれがある。

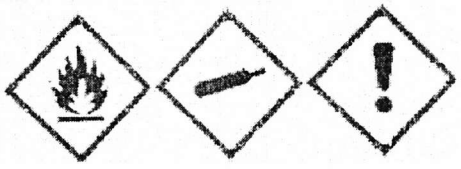
GHS分類

物理化学的危険性	可燃性・引火性ガス	区分1
	高圧ガス	圧縮ガスまたは深冷液化ガス
健康に対する有害性	特定標的臓器/全身毒性(単回暴露)	区分3(麻酔作用)
環境に対する有害性	水生環境有害性(急性)	区分3
	水生環境有害性(慢性)	区分3

記載がないものは分類対象外または分類できない

GHSラベル要素

絵表示



注意喚起語　:危険
危険有害性情報　:極めて可燃性/引火性の高いガス
高圧ガス　:熱すると爆発のおそれ
深冷液化ガス　:凍傷または負傷するおそれ
:眠気やめまいのおそれ
:水生生物に有害
:長期的影響により水生物質に有害

注意書き[安全対策]　:屋外または換気の良い場所でのみ使用すること。
:熱/火花/裸火/高温のもののような着火源から遠ざけること。
:粉じん/煙/ガス/ミスト/蒸気/スプレーを吸入しないこと。
:使用前に取り扱い説明書を入手すること。
:すべての安全注意を読み、理解するまで取り扱わないこと。
:指定された個人用保護具を使用すること。
:この製品を使用するときは、飲食または喫煙をしないこと。
:取り扱い後はよく手を洗うこと。
[応急措置]　:漏洩ガス火災の場合には、漏洩が安全に停止されない限り消火しないこと。安全に対処できるならば着火源を除去すること。
:吸入した場合、空気の新鮮な場所に移動し、呼吸しやすい姿勢で休息させること。
:暴露した場合、医師に連絡すること。
:気分が悪い時は、医師の診断/手当てを受けること。
[保管]　:施錠して保管すること。
:日光から遮断し、換気の良い場所で保管すること。
[廃棄]　:内容物や容器を都道府県知事の許可を受けた専門の廃棄物処理業者に業務委託すること。

3. 組成及び成分情報

単一製品・混合物の区別　:単一製品
化学名又は一般名(化学式):エチレン(C2H4)

成分及び含有量:

			官報公示番号		
化学物質	CASNo	分子量	化審法	安衛法	成分濃度
エチレン	74-85-1	28.00	適用外	適用外	99.9%以上

4. 応急措置

吸入した場合　:新鮮な空気の場所に移し、安静、保温に努め、医師に連絡する。
:呼吸が弱っている場合、加湿した純酸素を吸入させる。
:呼吸が停止している場合には人工呼吸を行う。
皮膚に付着した場合　:直ちに汚染された衣服や靴を脱ぎ、多量の水で充分に洗う。
目に入った場合　:多量の流水で注意深く洗眼し、直ちに医師の診断を受ける。
飲み込んだ場合　:口を大量の水ですすぐこと。直ちに医師の診断を受ける。
応急措置をする者の保護:漏出ガスが空気または酸素と混合し、燃焼、爆発を起こす危険を防ぐため、換気を行い拡散させること。
:このガスが漏洩または噴出している場所は、空気中の酸素濃度が低下している可能性があるので、換気を行い、必要に応じ陽圧自給式呼吸器を着用する。

5. 火災時の措置

消火剤　:自己火災の場合には、速やかにガスの供給を停止すること。
供給を停止できない場合は、噴霧散水しながら、このガス

がなくなるまで燃焼させるとともに、火災の拡大および類焼の防止に 努める。
:周辺火災に合わせた消火剤を使用する。
:容器の昇温を防ぐため、水で容器を冷却する。

使ってはならない消火剤:棒状注水
災時の特有の有害危険性:容器が火炎にさらされると内圧が上昇し、安全装置が作動し、このガスが噴出する。
:火災によって刺激性、または毒性のガスが発生するおそれがある。
:内圧の上昇が激しいときは、容器の破裂に至ることもある。容器弁が壊れたときなどは、容器はロケットのように飛ぶことがある。
:容器を安全な場所に搬出すること。搬出できない場合には、できるだけ風上から水を噴霧して容器を冷却すること。
:火が消えた後も漏洩が続く場合には、そのガスにより爆発を起こしたり、中毒により被害を拡大させる恐れがある。
:移動可能な容器は速やかに安全な場所に移すこと。

特有の消火方法 :火災を発見したら、まず部外者を安全な場所へ避難させる。
:漏洩が安全に停止されない限り、消火しないこと。
:安全に対処できるのならば、着火源を除去すること。
:危険でなければ火災区域から容器を移動する。
:ガスの滞留しない場所で風上より消火し、漏洩防止処置を施す。
:移動不可能な場合、容器及び周囲に散水して冷却する。
:消火後も、大量の水を用いて充分に容器を冷却する。
:漏洩部や安全装置に直接水をかけてはいけない。凍る恐れがある。
:消火活動は、有効に行える充分な距離から行う。
:周辺設備等の輻射熱による温度上昇を防止するため、水スプレーにより周辺を冷却する。
:周辺及び漏洩状況から判断して消火すると危険が増すと考えられるときは火災の拡大延焼を防止するため周辺に噴霧散水しながら容器内のガスが無くなるまで燃焼させる。

消火を行う者の保護 :適切な空気呼吸器、耐火手袋、耐火服等の保護具を着用し、火炎からできるだけ離れた風上から消火にあたる。

6. 漏出時の措置

人体に対する注意事項、保護具及び緊急時措置 :窒息の危険を防ぐため、窓や扉を開けて換気を良くすること。換気設備があれば、速やかに起動し換気する。
:大量の漏洩が続く状況であれば、漏洩区域をロープ等で囲み部外者が立ち入らないよう周囲を監視する。
:漏洩区域に入る者は、陽圧自給式呼吸器を着用すること。
:空気中の酸素濃度を測定管理すること。

環境に対する注意事項 :漏れた液には土、砂をかけるなど、周辺への流出を防ぎ、換気を充分にして蒸発させる。または散水し蒸発を促しても良い。この際、液体が下水、側溝、低所に入り込まないように注意すること。

回収、中和、封じ込め及び浄化の方法・機材　:漏洩したこのガスは換気を良くし、速やかに大気中に拡散、希釈させる。この物質は蒸発させてもよい。
二次災害の防止策　:漏出源を遮断し、漏れを止める。
人体に対する注意事項、保護具及び緊急時措置　:着火を防ぐため、全ての着火源を速やかに取り除くこと。
:排水溝、下水溝、地下室あるいは閉鎖場所への流入を防ぐ。
:漏洩物または漏洩源に直接水をかけない。
:風下の人を退避させ、漏出場所周辺は立入禁止とするとともに、火災爆発の危険性を警告する。
:高濃度では、窒息性のガスであるため、漏洩したガスが滞留しないように注意すること。
:適切な保護具(送気マスクまたは空気呼吸器、ゴーグル型保護眼鏡または防災面、耐薬品性手袋など)を着用し、風上から作業を行う。

7. 取扱い及び保管上の注意

取扱い上の注意

技術的対策　:低温で使用すると供給ガス組成が変化する可能性があり、低温での使用は注意すること。
:容器には、転落、転倒等を防止する措置を講じ、かつ粗暴な扱いをしないこと。倒れたとき、容器弁の損傷等により、高圧のガスが噴出すると、容器がロケットのように飛ぶことがある。
:容器の使用前に、容器の刻印、塗装(容器の表面積の1/2以上ねずみ色)、表示等によりガス名を確かめ、内容物が目的のものと異なるときには使用せずに、販売元に返却すること。
:容器弁の開閉に使用するハンドルは所定の物を使用し、容器弁はゆっくり開閉すること。
:開閉に際し、ハンマー等でたたいてはならない。手で開閉ができないときは、その旨明示して、販売者に返却すること。
:容器から直接使用しないで、必ず圧力調整器を使用すること。
:圧力調整器の取り付けにあたっては、容器弁のネジ方向を確かめてネジにあったものを使用すること。
:圧力調整器を正しい要領にて取り付けた後、容器弁を開ける前に、圧力調整器の圧力調整ハンドルを反時計方向に回してゆるめ、その後、ゆっくりと容器弁を開く。この作業中は、圧力調整器の側面に立ち、正面や背面に立たないこと。
:継手部、ホース、配管および機器に漏れがないか調べること。漏洩箇所の検査には、石けん水等の発泡液による方法が簡単、安全で確実である。
:作業の中断あるいは終了後、作業場所を離れるときは、容器弁を閉じる。その後、圧力調整器内のガスを出し、圧力調整ハンドルをゆるめておくこと。
:容器を電気回路の一部に使用しないこと。特に、アーク溶接時のアークストライクを発生させたりして損傷を与えないこと。
:容器弁等が氷結したときは、4。℃以下の温水で温め、バーナー等で直接加熱しないこと。

:このガスを多量に使用する場合には、使用量によって集合装置等の供給設備が特別に設計、製作されることがある。使用者は、これらの設備・機器の正しい操作方法や使用方法について、製造者または販売者から指導を受け、取り扱い説明書および指示事項に従うこと。

局所排気　:このガスを使用するにあたっては、麻酔作用とともに空気中の酸素濃度が全体換気低くなる危険性がある。また、強い引火性があることから、密閉された所や換気の悪い所で取り扱わないこと。

:このガスを使用する設備の安全弁の放出口は、排出されたガスが滞留しないように、安全な場所に放出口を設置すること。

:このガスを使用するタンク類の内部での作業は、十分な換気を行い、労働安全衛生法に従い行うこと。

注意事項　:脱着式の保護キャップは、使用前に取り外すこと

:容器を使用しないときは、脱着式の保護キャップを確実に取り付けること。

:容器には、充てん許可を受けた者以外はガスの充てんを行なってはならない。

:容器の修理、再塗装、容器弁および安全装置の取り外しや交換等は、容器検査所以外では行わないこと。

:容器の刻印、表示等を改変したり、消したり、剥したりしないこと。

:容器をローラーや型代わり等の容器本来の目的以外に使用しないこと。

:容器の授受に際しては、あらかじめ容器を管理する者を定め、容器を管理すること。

:契約に示す期間を経過した容器および使用済みの容器は速やかに販売者に返却すること。

:このガスを、圧縮空気や空気の代わりに使用しないこと。

:高圧ガス保安法の定めるところにより取り扱うこと。

安全取扱い　:容器弁の口金内部に付着した塵挨類を除去する目的でガスを放出する場合には、口金を人のいない方向に向けて、

注意事項　ガス出口弁を短時間微開して行うこと。

:高圧のガスが直接人体に吹きつけられると、損傷を起こすことがあるので・高圧で噴出するガスに触れないこと。

:容器の圧力は0.1MPa以上残し、使用後は確実に容器弁を閉めた後、保護キャップを付けて、速やかに残ガス容器置場に返すこと。

:容器にこのガス以外のガスが入った可能性があるときは、容器記号番号等の詳細を販売者に連絡すること。

:可燃性ガスであるので、火気の近くで使用しないこと。

:このガスは、可燃性であり、空気や酸素と混合すると燃焼・爆発の危険性がある。

保管上の注意

適切な　:熱、火花、裸火のような着火源から離して保管すること。

一禁煙。

保管条件　:換気の良い場所で保管すること。

:酸化剤、酸素、爆発物、ハロゲン、圧縮空気、酸、塩基、

食品化学品等から離して保管する。
:容器置場の周囲2m以内には、必要な障壁を設けた場合を除き、火気または引火性もしくは発火性の物を置かないこと。
:容器置場には、消火設備を設けること。
:火炎やスパークから遠ざけ、火の粉等がかからないようにすること。
:電気配線やアース線の近くに保管しないこと。
:水はけの良い、換気の良好な乾燥した場所に置くこと。
:腐食性の雰囲気や、連続した振動にさらされないようにすること。
:直射日光を受けないようにし、温度40℃以下に保つこと。

安全な容器
包装材料　:高圧ガス容器として製作された容器であること。

8. 暴露防止及び保護措置

設備対策　:防爆仕様の局所排気を設置する。

許容濃度　:日本産業衛生学会(2008年版)　:設定されていない。
ACGIH(2008年版)TLV-TWA　:200ppmA4

保護具

呼吸器の保護具	:必要により空気呼吸器、酸素呼吸器、送気マスク
手の保護具	:革手袋
目の保護具	:保護面、保護眼鏡
皮膚及び身体の保護具	:誘電性安全靴・作業衣を着用すること。

9. 物理的及び化学的性質

外観	:無色で気体または液体
臭い	:特殊な甘い臭い
pH	:該当しない
融点・凝固点	:−169.2℃(融点)
沸点、初留点及び沸騰範囲	:−103,7℃(沸点)
引火点	:−136℃
自然発火温度	:543℃
燃焼又は爆発範囲の上限/下限	:2.7〜36.0vol%
蒸気圧	:8100kPa(15℃)
蒸気密度	:0.98
比重(相対密度)	:0.00126(0℃)
溶解度	:131mg/L(25℃水) アセトン、ベンゼンに可溶
オクタノール/水分配係数	:log Pow=1.13(測定値)
分解温度	:データなし

10. 安定性及び反応性

安定性・危険有害　:高温の物体との接触面、火花または裸火により発火する。比較的弱い

反応可能性	エネルギーの静電気花火で発火が起こりうる。 :600℃以上の温度下で重合し、芳香族化合物を生成することがある。 :強力な酸化剤と反応し、火災や爆発の危険をもたらす。
避けるべき条件	:高温の物体、火花、裸火、静電気火花。
混触危険物質	:強酸化剤。
危険有害な分解生成物	:燃焼したとき、一酸化炭素、二酸化炭素の有害ガスが発生する。

11. 有害性情報

急性毒性(吸入) :ヒト LCL。(5分) =950,000ppm(酸素との混合ガス)
マウス LC5。 =950,000ppm(95%)
マウス麻酔作用の現れる時間 800 mg/l(75%) 5分
920 mg/l(80%) 3分
1,050 mg/l(80%) 1分

慢性毒性・長期毒性(吸入) :ラット(F-344) 濃度0、300、1,000、3,000ppm各群120匹
6時間/日、5日/週、24ヶ月被毒の兆候等現れず。
:ラット(アルビノ) 濃度0,300,1,000,3,000ppm各群120匹
6時間/日、5日/週、24ヶ月被毒の兆候等現れず。

がん原生 :ラット(F-344) 濃度最高3,000ppm6時間/日、5日/週、24ヶ月発がんは認められず。IARCモノグラフによれば、グループ3〔がん原生の分類ができない〕に分類する。

変異原性 :大腸菌および数種の枯草菌で、変異原性はみられない。

その他(吸入) :犬;血中エチレン量は、吸入ガス濃度に関係し、66～77.5%(=760～89。g/m3)の濃度で、血中100mlに8～10mlのエチレンガスが含まれる。血中からの排泄は2分以内に現れ、回復はかなり早い。

12. 環境影響情報

生態毒性 :情報なし

魚毒性 :水棲生物、急性毒性TLm(96時間) 100～1,000ppm

その他 :植物への影響;植物に対する生理作用は極めて広く、気相中濃度0.01～0.1ppmで影響が現れ、通常1～5ppmで最大の効果を示す場合が多い。生理作用としては伸長、生長の促進または阻害、開花の促進または阻害、花色の退色、落葉の促進、果実の成熟促進、たんぱく質・核酸の合成促進、その他報告されている。

13. 廃棄上の注意

:使用済み容器はそのまま容器所有者に返却すること。
:容器に残ったガスは、みだりに放出せず、圧力を残したまま容器弁を閉じ、製造者または販売者に返却すること。
:容器の廃棄は、容器所有者が行い、使用者が勝手に行わないこと。

14. 輸送上の注意

危険物輸送に関する国連分類及び国連番号

国連分類 :クラス2.1(引火性高圧ガス)

国連番号　　:1962(圧縮) 1038(液化)

国内規制

高圧ガス保安法　　:法第2条(可燃性ガス、圧縮ガス、液化ガス)

海上輸送

船舶安全法　　:危規則第3条危険物告示別表1高圧ガス(引火性)

航空輸送

航空法　　:施行規則第194条告示別第1高圧ガス(D一旅禁)

道路法　　:施行令第19条の13車両の通行の制限

追加の規制/その他　　:応急措置指針番号;115(液化されている物)
:応急措置指針番号:川(圧縮されている物)

特別の安全対策　　:高圧ガス保安法における規定に基づき安全な輸送を行う。
:移動時の容器温度は40℃以下に保つ。特に夏場はシートをかけ温度上昇の防止に努める。
:容器に衝撃が加わらないように、注意深く取り扱う。
:移動中の容器の転倒、バルブの損傷等を防ぐための必要な措置を施すこと。
:車両等により運搬する場合は、イエローカード、消火設備および応急措置に必要な資材、工具を携行する。
:酸素ガスと混載するときは、容器弁の方向を反対に向けるか、間隔を十分にとること。

15. 適用法令

高圧ガス保安法　　:法第2条(可燃性ガス、圧縮ガス、液化ガス)

労働安全衛生法　　:施行令別表第1危険物(可燃性のガス)

航空法　　:施行規則第194条告示別表第1高圧ガス(D一旅禁)

港則法　　:施行規則第12条危険物高圧ガス

船舶安全法　　:第3条危険物告示別表第1高圧ガス(引火性)

道路法　　:施行令第19条の13車両の通行の制限別表2-2

16. その他の情報

適用範囲　　:この化学物質等安全データシートは、エチレン(可燃性)に限り適用するものである。

引用文献　　:1) ILO:Occupational Exposure Limits for Airbone Toxic, Substances. 2nd. Ed. (1980),
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その他　　:記載内容は現時点で入手できた資料や情報に基づいて作成しておりますが、記載のデータや評価については、情報の完全さ、正確さを保証するも

ではありません。また、記載事項は通常の取扱いを対象としたものですので、特別な取扱いをする場合には新たに用途・用法に適した安全対策を実施の上、お取扱い願います。

資料　3

エチレンによる馬鈴しょの萌芽抑制効果に関する試験

（平成 19 年秋～20 年夏、酪農学園大学）

1. 目　的

ポテトチップス加工用馬鈴しょは低温貯蔵を行うと糖が増加し、油加工時の外観品質の低下を招くため、10℃前後の高温で貯蔵されている。そのため、貯蔵中に萌芽し、芽が著しく伸長し、加工時の芽の除去、除去した芽の処理、製品歩留の低下、品質の劣化など様々な問題がある。

本試験は、植物ホルモンであるエチレンを用いることにより馬鈴しょの萌芽および芽の伸長を抑制する長期貯蔵技術を確立し、国内産加工用馬鈴しょ原料を高品質で周年供給できる体制を構築する。

2. 試験方法

１）供試材料

平成19年、帯広市川西産「きたひめ」、「スノーデン」を用いた。

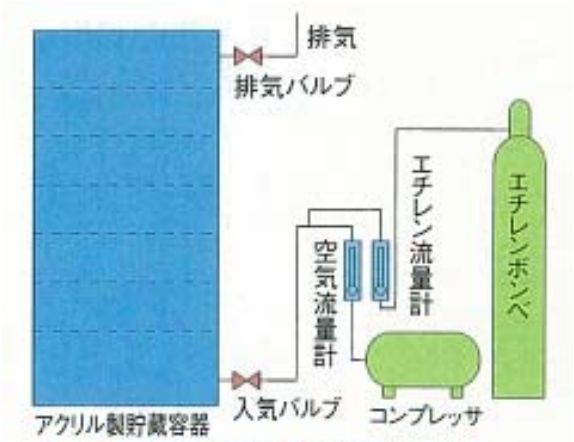
２）エチレンの供給と貯蔵方法

(1)エチレンの供給装置

内寸560㎜×483㎜×986㎜のアクリル製ガス置換デシケータを貯蔵容器として用いた。

デシケータの下部からエチレン混合空気を供給し、上部から排出することによりエチレン供給および馬鈴しょの呼吸による二酸化炭素除去を行った。

エチレン混合空気は、コンプレッサーによる圧縮空気とボンベ入りエチレン１％含有窒素ガスとをそれぞれロータメータにより流量調節後に混合してデシケータに供給した。



図－１　エチレン供給貯蔵実験装置


写真１：恒温室内にデシケータを設置


写真２：デシケータ内の「きたひめ」

写真３：デシケータ内の「スノーデン」

写真４：エチレンと空気の流量計

写真５：コンプレッサー

写真６：エチレンガスボンベ

(2)貯蔵方法

各品種120個の試料（平均約150g）をデシケータ内にランダムに置いて貯蔵を行った。貯蔵容器を8℃に設定した恒温室内に設置した。無処理区はダンボールに20個ずつ試料を入れて貯蔵庫に置いた。

３)測定項目

貯蔵環境の温湿度およびエチレン濃度については、貯蔵期間中継続して測定した。試料の品質については、貯蔵開始2ヵ月後から1ヶ月間隔で測定した。

(1)恒温室および貯蔵庫内の温湿度

恒温室および貯蔵庫内の温湿度は、データーロガーを用いて測定した。

(2)デシケータ容器内のエチレン濃度

ガスタイトシリンジによりデシケータ容器の上下2箇所から容器内ガスを採取し、ガスクロマトグラフを用いてエチレン濃度を測定した。

(3)試料質量、水分含量

電子天秤を用いて試料質量を測定し、質量減少率を求めた。水分含量は70℃24時間恒温乾燥法により求めた。

(4)芽の長さ

5mm以下、5mm以上の芽の塊茎当たりの個数、塊茎毎の最長芽の長さ、塊茎当たりの芽の

質量を測定した。

(5)糖含量

HPLCを用いてショ糖、ブドウ糖、果糖含量を測定した。

(6)硬度

レオメータを用い、直径2mmの円筒状プランジャを50mm/sの速度で貫入させて荷重を測定した。

(7)ポテトチップカラー

試料を約1mmの厚さにスライスし、180℃のサラダオイルで約120秒間フライし、その色をアグトロンメーター（数値は、小さいほどポテトチップカラーは淡くなる、以下、同様）を用いて測定した。

3. 結果および考察

図１に、デシケータ容器内のエチレン濃度の推移を示す。エチレン濃度の計算上の設定値を5ppmとして貯蔵開始したが、貯蔵開始から約40日間は約2ppmで推移した。

その後エチレン濃度の設定を上げて4ppmとなるように調節を行った。これにより濃度は上昇し、多少の変動はあるものの4～6ppmで推移した。

このエチレン供給装置は、試料ガス採取、測定、濃度調節はいずれも手動によるため、精密な制御はできなかったが、ほぼ想定した濃度を得ることが可能であった。

貯蔵環境の温度・湿度は、エチレン処理区で平均 8.2℃、95%、無処理区で 7.4℃、84%であった。

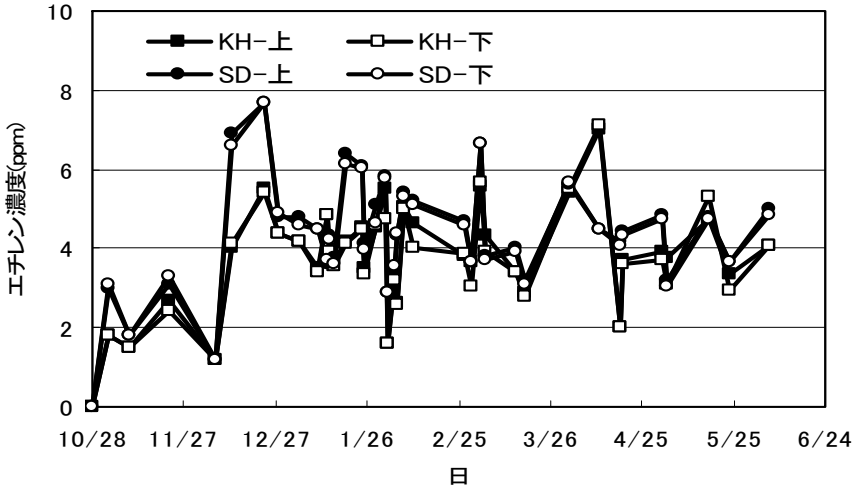


図1 エチレン濃度の推移

図2に、最長芽の長さの平均値の推移を示す。

いずれの品種も12月28日までは萌芽が見られなかったが、その後萌芽が開始した。

7月4日のエチレン処理区では、「きたひめ」の最長芽は23mm、「スノーデン」では14mm、無処理区では、それぞれ約200mm、250mmであった。

エチレン処理区は無処理区より平均温度が約0.8℃高く推移したにもかかわらず、エチレンによる芽の生長抑制効果は明らかであった。

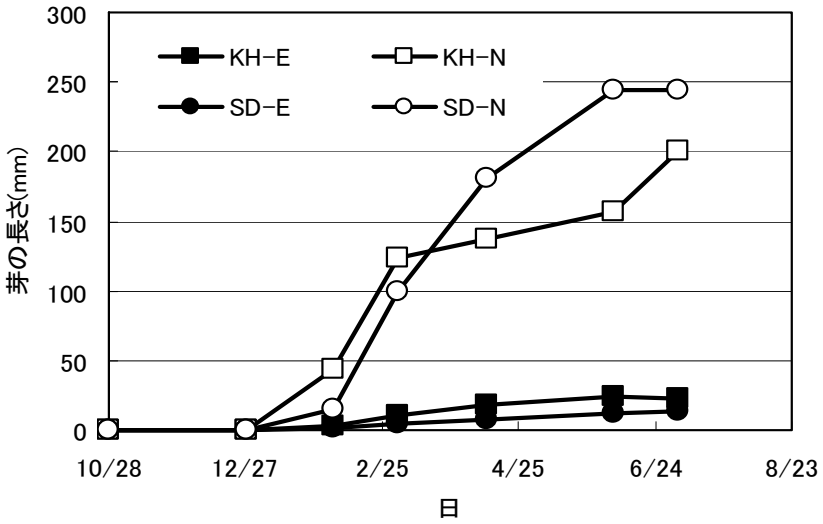


図2 最長芽の長さの平均値

図3に、塊茎の損失率の推移を示す。

損失率は芽を含む塊茎の質量減少率に初期塊茎の質量に対する芽の質量百分率を加えた値で示した。

温湿度環境が異なるため単純な比較はできないが、芽が大きく生長することによって損失も増大し、「スノーデン」の無処理区では35%にまで達し、萌芽抑制によって損失も低く抑えられた。

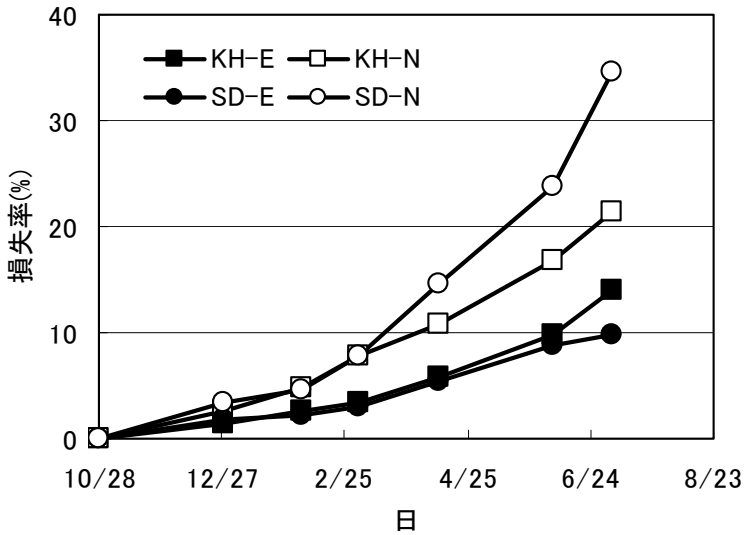


図3 塊茎の損失率

図4に、還元糖含量の推移を示す。

「きたひめ」は貯蔵開始後、無処理区で大きく増加し、その後徐々に低下して4月初旬以降、エチレン区とほぼ同等になった。

その後はいずれも変化が小さく、0.1g/100gFW程度となった。「スノーデン」では貯蔵開始後エチレン処理区での増加が顕著であったが、その後低下し3月初旬には無処理区と同等になった。

4月初旬以降両区とも急激に増加したが、エチレン処理区は無処理区と同等あるいはやや少なく推移した。

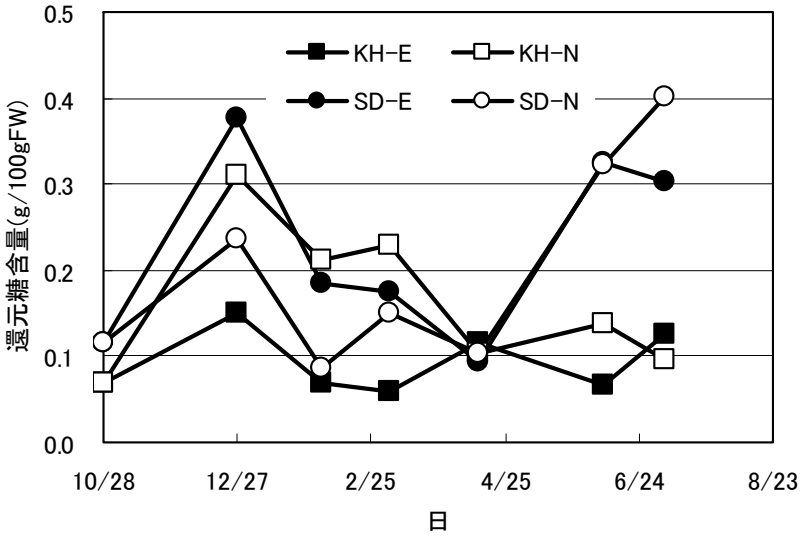


図4 還元糖含量の推移

図 5 に、ポテトチップカラーの推移を示す。

還元糖の増加が大きかった「きたひめ」の無処理区は、ポテトチップカラーの値が低く推移した。

無処理区でポテトチップカラーが低下したのは、貯蔵温度が低かったことが原因と考えられる。

「スノーデン」は、貯蔵初期においてエチレン処理区が無処理区と比較してやや低い値を示したが、2 月初旬以降無処理区と逆転した。

「スノーデン」の無処理区では、萌芽による塊茎の萎縮が顕著であり、貯蔵後期には塊茎周辺部分に黒変が見られ、ポテトチップカラーにも影響した。

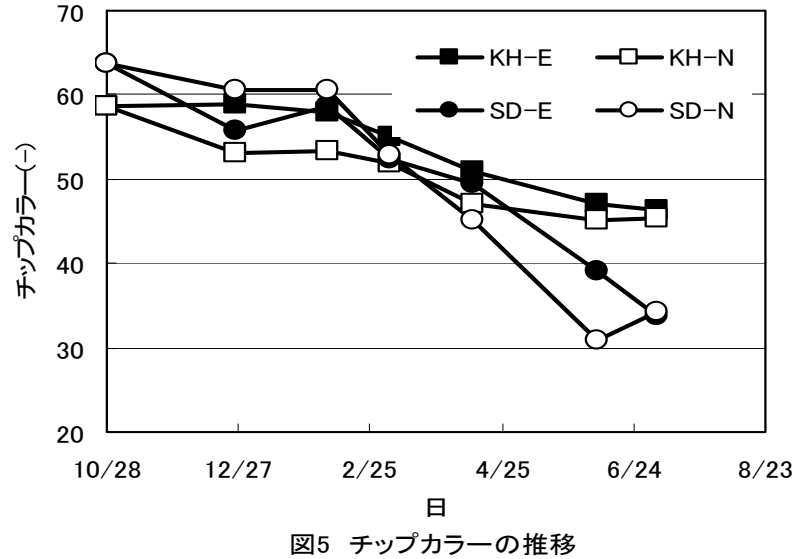


図5 チップカラーの推移

4. まとめ

定濃度エチレン環境下で貯蔵することにより、顕著に馬鈴しょの萌芽および芽の伸長を抑制することが可能であった。

還元糖含量は低レベルに抑制でき、ポテトチップカラーも無処理区と同等以上であった。

資料　4

エチレンによる馬鈴しょの萌芽抑制効果に関する試験

（平成 20 年秋～21 年夏、酪農学園大学）

１．目　的

加工用馬鈴しょ原料の貯蔵中の萌芽および芽の伸長を抑制し、国産馬鈴しょの周年供給体制を確立することを目的とし、代表的な 3 品種を用いてエチレンによる芽の生長抑制効果を明らかにするとともに、加工適性の評価を行った。

２．試験方法

１）供試材料

平成 20 年、帯広市川西産「きたひめ」、「スノーデン」、「トヨシロ」を用いた。

２）エチレンの供給方法および濃度

ガス置換デシケータを利用したエチレン供給貯蔵基礎実験装置を用いた（参考資料１を参照）。

エチレンの供給は 10 月 28 日から開始し、エチレン濃度は 4ppm とした。

昨年度は空気およびエチレン供給は連続としたが、今年度はタイマーを用いて間欠供給とした。

３）貯蔵方法

エチレン処理区および無処理区は同様の貯蔵容器（デシケータ）を用いた（参考資料１を参照）。貯蔵容器内の温度は 8℃、湿度は約 85％であった。

４)測定項目

貯蔵環境の温度・湿度、エチレン濃度については、貯蔵期間中継続して測定した。

品質については、10月28日、12月26日、2月16日、3月20日、4月24日、5月29日、7月3日に測定した。

(1)恒温室内温湿度

恒温室内温湿度をデーターロガーを用いて測定した。

(2)貯蔵容器内（デシケータ）エチレン濃度、二酸化炭素濃度

ガスタイトシリンジにより貯蔵容器の上下２箇所から容器内ガスを採取し、ガスクロマトグラフを用いてエチレン濃度および二酸化炭素濃度を測定した。

(3)試料質量、水分含量

電子天秤を用いて試料質量を測定し、質量減少率を求めた。水分含量は70℃24時間恒温乾燥法により求めた。

(4)芽の長さ

5㎜以下、5㎜以上の芽の塊茎当たりの個数、塊茎毎の最長芽の長さ、塊茎当たりの芽の

質量を測定した。

(5)糖含量

HPLCを用いてショ糖、ブドウ糖、果糖含量を測定した。

(6)硬度

レオメータを用い、直径2㎜の円筒状プランジャを50㎜/sの速度で貫入させて荷重を測定した。

(6)ポテトチップカラー

試料を約1㎜の厚さにスライスし、180℃のサラダオイルで約120秒間フライし、その色をアグトロンメーターを用いて測定した。

３．結果

図 1～3 に、貯蔵中エチレン濃度の推移を示す。

「きたひめ」、「スノーデン」の貯蔵初期のエチレン処理区において、急激なエチレン濃度の上昇があったが、これはコンプレッサの不調により空気の供給が停止したためである。また、このとき無処理区においてもエチレンが一時的に検出された。これ以外ではいずれもほぼ設定どおりにエチレンを制御することができた。

貯蔵開始当初は 1 時間換気、5 時間休止のサイクルで換気およびエチレンの供給を行っていたが、特に、エチレン処理区において CO_2 濃度の上昇が見られたため、「きたひめ」、「スノーデン」では 2 時間換気、4 時間換気に、「トヨシロ」においては、3 時間換気 3 時間休止に変更することにより CO_2 濃度は 0.1%以下に抑えることができ、以後このサイクルで行った。

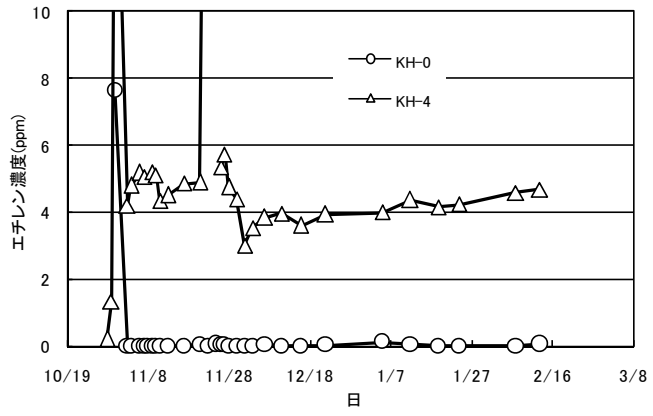


図1 貯蔵中エチレン濃度の推移(きたひめ)

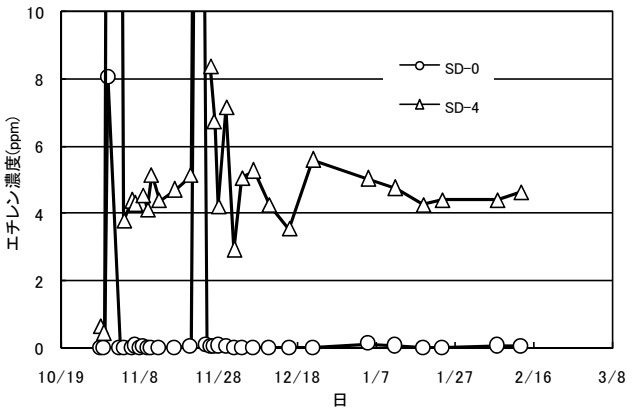


図2 貯蔵中エチレン濃度の推移(スノーデン)

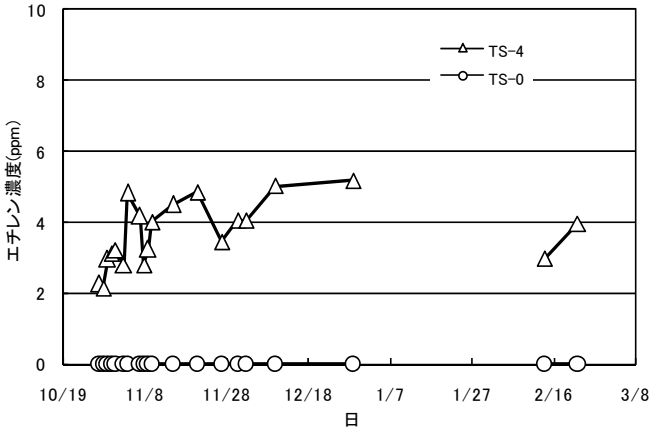


図3 貯蔵中エチレン濃度の推移(トヨシロ)

図 4～6 に、塊茎毎の最長芽の長さの平均値の推移を示す。

いずれの品種においても 2 月 16 日の時点で萌芽が見られ、特に、無処理区において芽の伸長が大きかった。

貯蔵終了時点では、いずれの品種においてもエチレン処理区では芽の長さが 20㎜ 以下に抑制された。

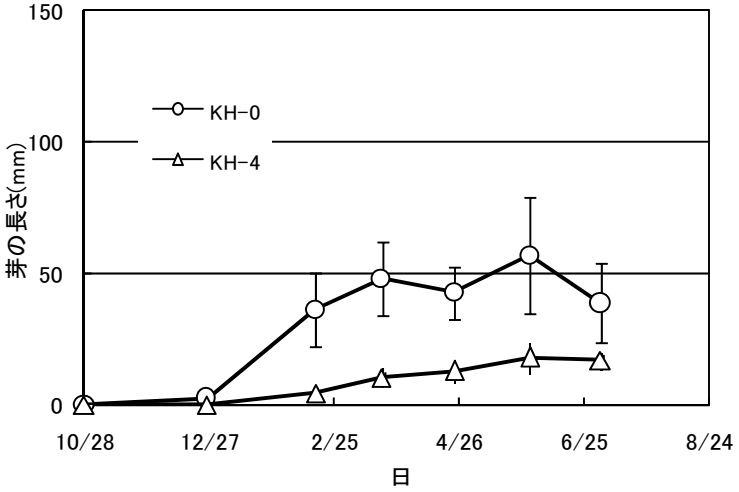


図4 最長芽の長さの推移(きたひめ)

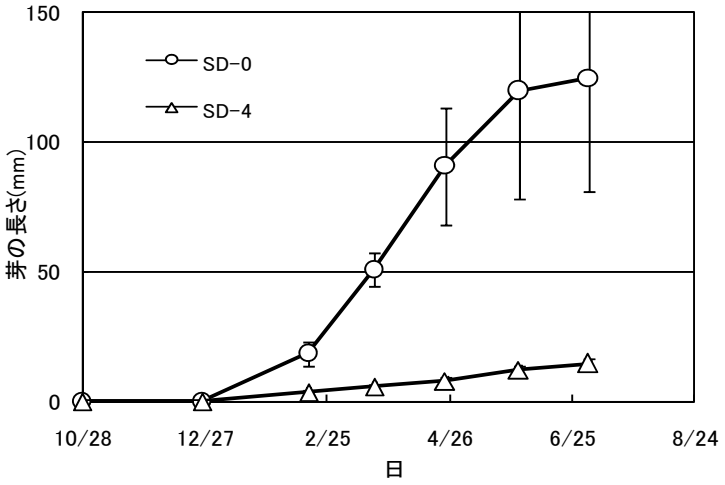


図5 最長芽の長さの推移(スノーデン)

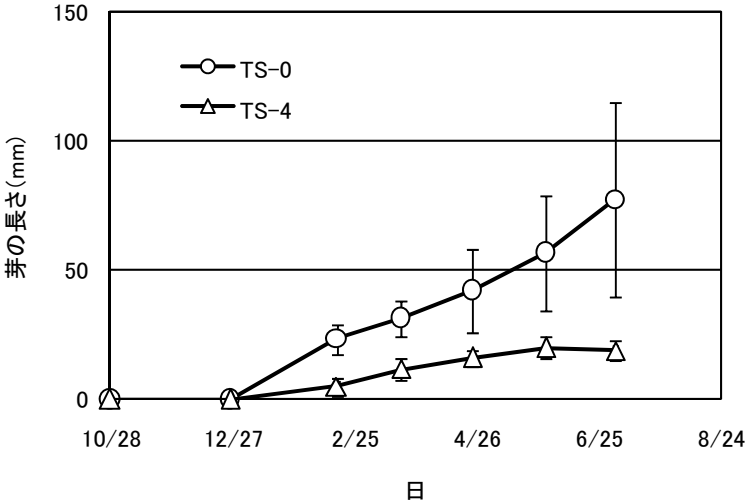


図6 最長芽の長さの推移(トヨシロ)

図 7～9 に、還元糖含量の推移を示す。

いずれの品種も貯蔵初期に還元糖が増加し、その後低下する傾向にあり、貯蔵末期に再び増加する傾向がみられた。

「トヨシロ」においては、エチレン処理区で還元糖の増加が大きかった。「トヨシロ」は無処理区においても還元糖の増加が大きいが、これは貯蔵温度を 8℃と通常より低温に設定したためと考えられる。

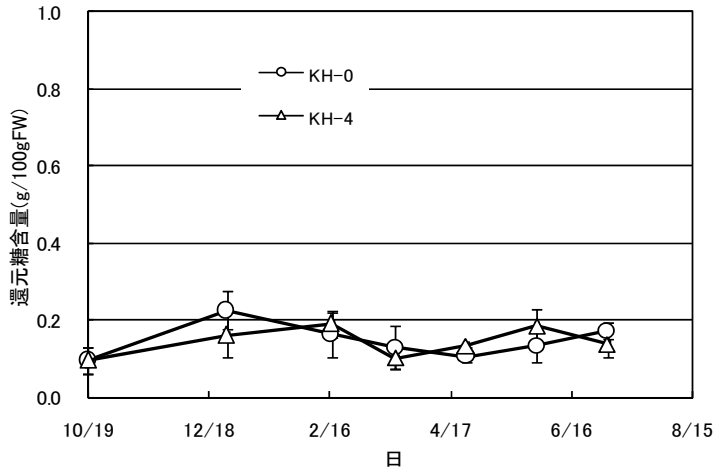


図7 還元糖含量の推移(きたひめ)

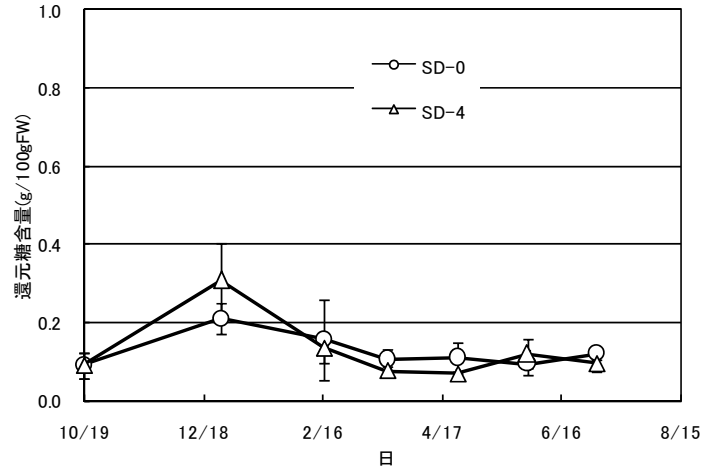


図8 還元糖含量の推移(スノーデン)

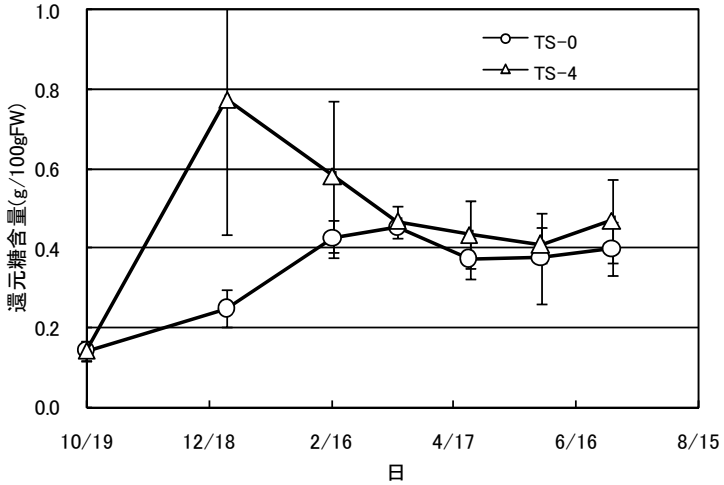


図9 還元糖含量の推移(トヨシロ)

図 10～12 に、ポテトチップカラーの推移を示す。

還元糖含量の推移を反映し、貯蔵初期にポテトチップカラーが低下し、その後回復する傾向にあるが、「きたひめ」は低下の度合いが小さい。また、貯蔵末期に低下する傾向にあった。

「トヨシロ」はポテトチップカラーの低下は回復しておらず、原料として使用できるレベルにない。

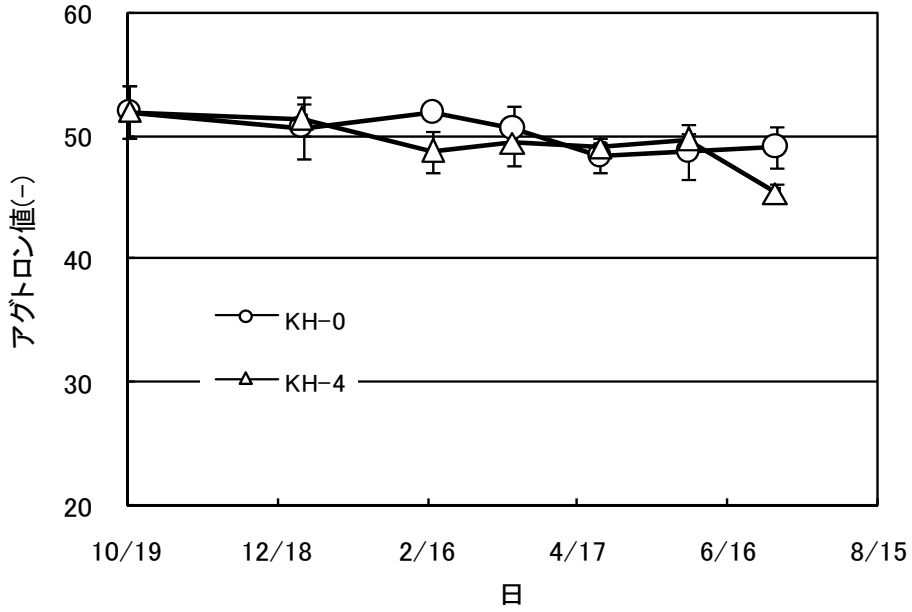


図10 チップカラーの推移(きたひめ)

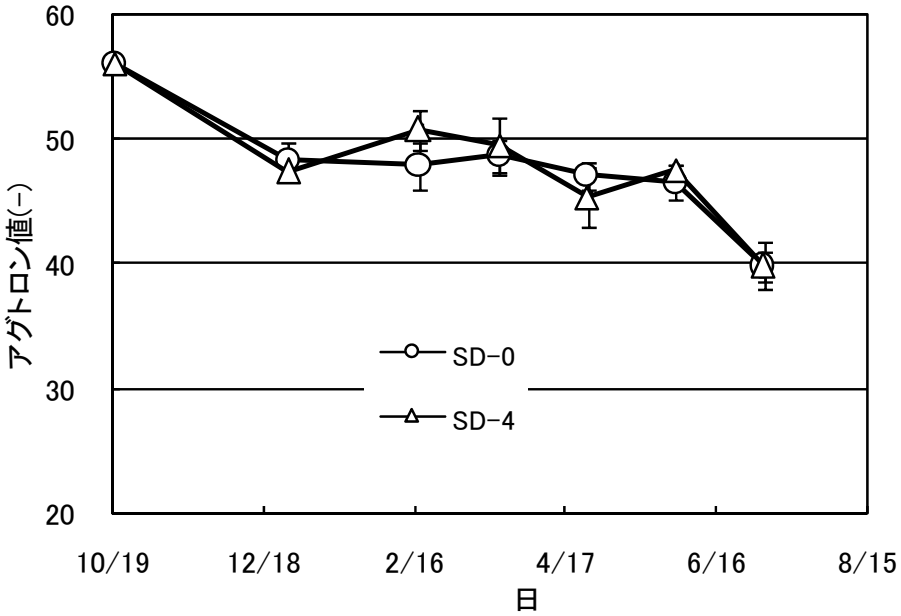


図11 チップカラーの推移(スノーデン)

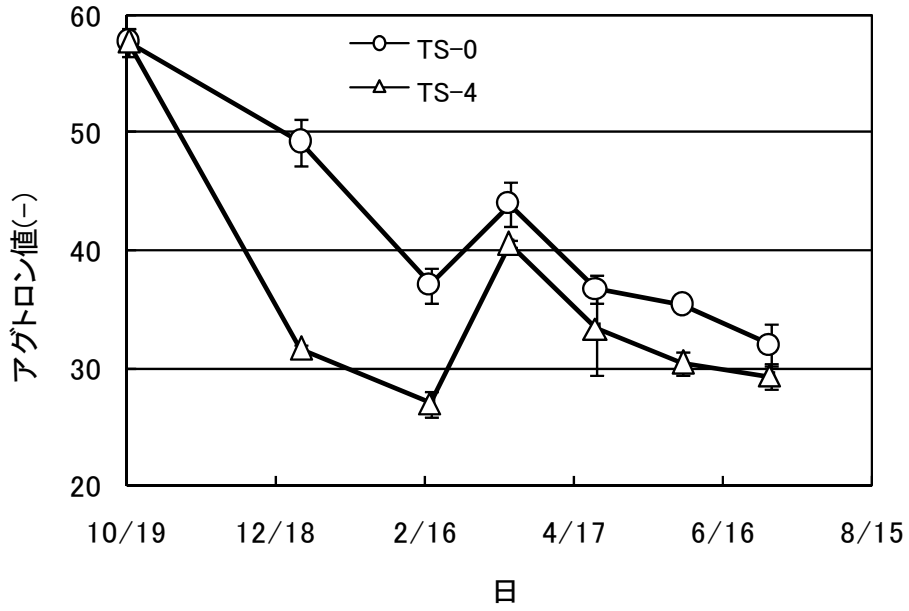


図12 チップカラーの推移(トヨシロ)

４．要約

いずれの品種においても芽の伸長は顕著に抑制することができた。

ポテトチップカラーは「きたひめ」、「スノーデン」については、エチレン処理による大きな低下は認められなかった。

「トヨシロ」については、エチレン処理の効果は明らかであったが、貯蔵温度が低いことによってポテトチップカラーの低下が著しく、特に、エチレン処理による貯蔵初期の低下が大きかった。

資料　５

エチレンによる馬鈴しょの萌芽抑制効果に関する試験

（平成 20 年秋～21 年夏、十勝農業試験場）

１．目　的

酪農学園大学におけるエチレンによる長期貯蔵中の加工用馬鈴しょの萌芽を抑制する試験成果を受けて、エチレン供給装置を試作し、JA 士幌町において、実用化のための萌芽抑制効果および品質保持効果を検証する。

２．試験方法

１）試験の実施場所は JA 士幌町（北海道河東郡士幌町）、試験の担当は十勝農業試験場（北海道河西郡芽室町）である。

２）供試材料：平成 20 年、士幌町産の「トヨシロ」、「きたひめ」、「スノーデン」で、各品種 200 kgを供試した（各品種、約 20kg 入りミニコンテナ 10 個を使用）。

３）貯蔵庫

貯蔵庫は 3 室を使用した。床面積は約 2 坪である。

貯蔵庫内の温度は 8℃、湿度は 85%に制御した。

(1) 1 号室：エチレン処理区（二酸化炭素は 0.2%以下、酸素は 18%以上に制御した。以上、以下になったら自動的にダンパーが開閉する）

(2) 2 号室：無処理区（二酸化炭素、酸素は無制御）

(3) 3 号室：エチレン処理区（二酸化炭素、酸素は無制御）

４）エチレン

(1) エチレンの供給開始は 12 月 3 日である。

(2) エチレンの濃度は、12 月 3 日～12 月 9 日は 2ppm、12 月 10 日～12 月 16 日は 4ppm と順次濃度を上げ、12 月 17 日からは 8ppm とした。

(3) エチレンの供給装置

フジプラント株式会社と三菱電機冷熱プラント株式会社の協同製作による特注品

写真 1. 実験棟の内部、左側に貯蔵庫 1、2、3 室 正面奥にコンロトール盤

写真 2. 貯蔵庫内、ミニコンを 4 段

写真 3. 貯蔵庫の内部

写真 4.実験庫内部、
加湿噴霧の状態

写真 5.庫内のセンサー

写真 6.エチレン、酸素、二酸化炭素、温度、湿度のコントロール盤

写真 7.プラントフロー
エチレン、二酸化炭素、酸素、
湿度、温度の表示盤

写真 8.二酸化炭素、エアー
ポンプの表示ランプ

写真 9.エチレン
ガスボンベ

５）萌芽調査

萌芽した芽の長さを 0㎜（無）、1～５㎜、６～10 ㎜、10～20 ㎜、21 ㎜以上の５区分に分けて塊茎数を調査した。

６）品質の調査

貯蔵前、貯蔵中（3 月）、試験終了時(7 月)について、糖含量、ポテトチップカラーを調査した。

３．結　果

エチレン処理区については、二酸化炭素と酸素の無制御（3 号室）の試験結果は、制御（1 号室）と同様であったので、ここでは制御の貯蔵庫（１号室）から得られたデータについて述べる。

無処理区では、「トヨシロ」で１月下旬、「きたひめ」で１月上旬、「スノーデン」で２月上旬より萌芽は始まった。

エチレン処理区では、「トヨシロ」は３月より、「きたひめ」は１月下旬より萌芽している塊茎がみられた。「スノーデン」は萌芽はしているものの、10 ㎜を超えたものは無かった。「トヨシロ」、「きたひめ」ともに徐々に芽は伸びているが、芽長は短く 20 ㎜を超えたものは少なく、伸びても 30 ㎜以下であった。

いずれの品種もエチレン処理による萌芽抑制効果は明らかに認められた。

エチレン処理をした塊茎の芽の形状には、品種間差異が見られた。

「トヨシロ」は芽は伸びないが、小さい芽が多数発生しカリフラワー状となった。「きたひめ」は団子状の芽となり、非常に脱落しやすかった。「スノーデン」は「トヨシロ」に似て芽

の数は増加しているが、芽の伸びは一番少なく、10 ㎜を超えるものは無かった。

写真１：「トヨシロ」（無処理区）

写真２：「トヨシロ」（処理区）

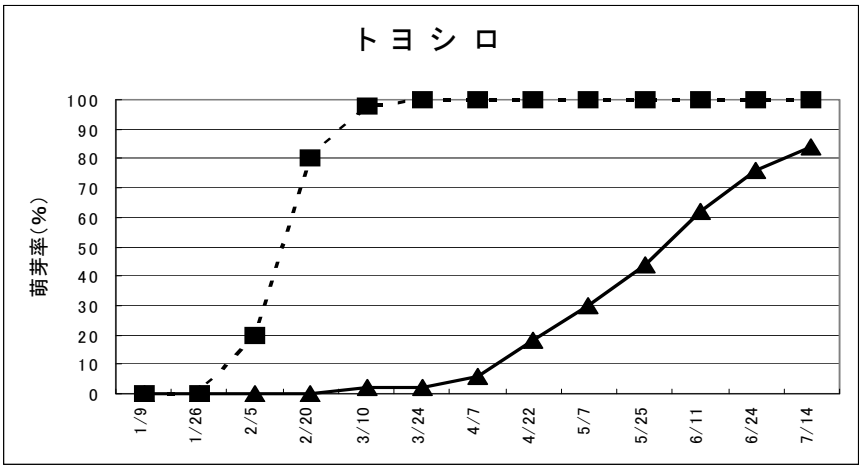
写真３：「きたひめ」（無処理区）

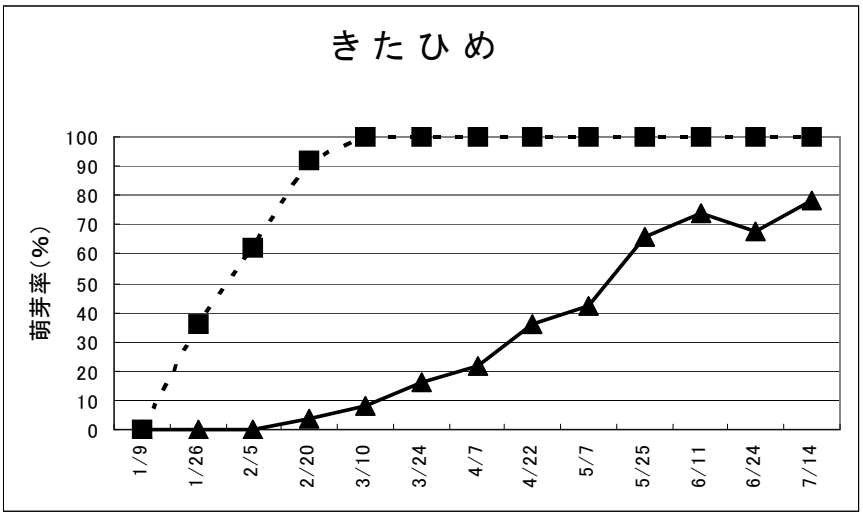
写真４：「きたひめ」（処理区）

写真５：「スノーデン」（無処理区）

写真６：「スノーデン」（処理区）

図１．エチレン無処理区と処理区の芽の状況（平成 21 年 4 月 22 日）





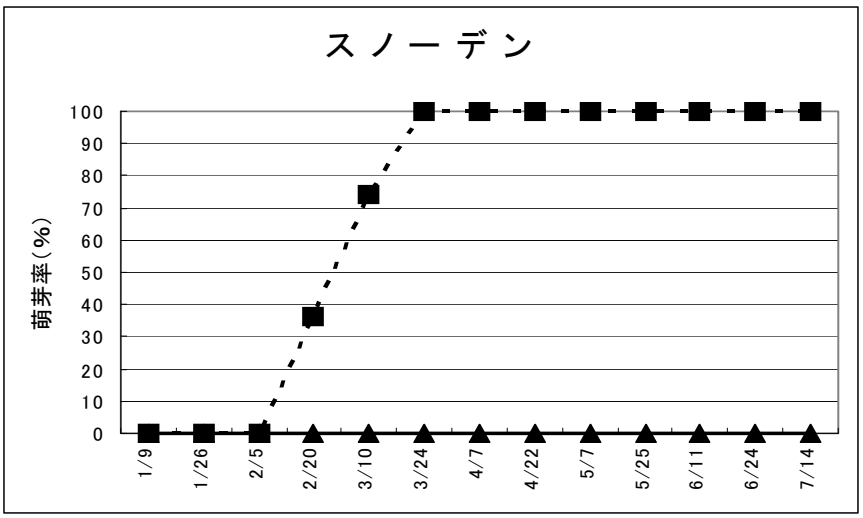


図１．エチレン処理における萌芽率の推移

▲ ———— 処理区

■ ---------- 無処理区

注）萌芽率は、芽の長さ 10 ㎜以上の割合を示す

表１．７月 14 日時点の萌芽の状況（数値は個数割合%）

芽長（㎜）	0	～5	5～10	10～20	20～
トヨシロ	0	0	16	74	10
きたひめ	4	4	14	60	18
スノーデン	0	22	78	0	0

要約：20 ㎜を超えるものでも 30 ㎜に達している塊茎はない

写真 1.「トヨシロ」の芽の長さ
左：処理区、右：無処理区

写真 2.「トヨシロ」の処理区芽の形状

写真 3.「きたひめ」の芽の長さ
左：処理区、右：無処理区

写真 4.「きたひめ」の処理区芽の形状

写真 5.「スノーデン」の芽の長さ
左：処理区、右：無処理区

写真 6.「スノーデン」の処理区芽の形状

図２．７月 14 日時点の芽の伸びと形状

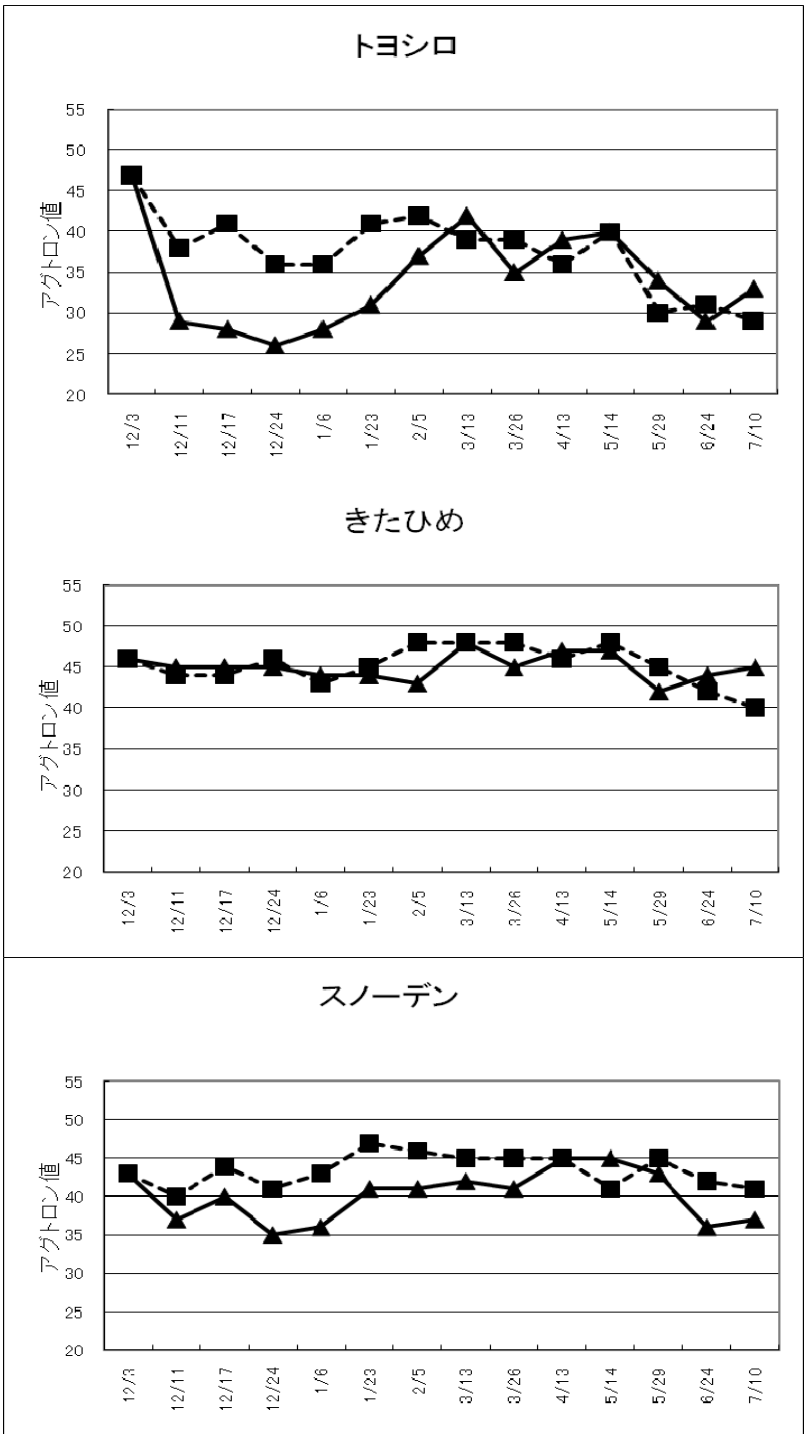


図３．ポテトチップカラーの推移

（▲：処理区、■：無処理区、アグトロン値は多いとカラーは淡くなる）

４．ポテトチップカラー

「トヨシロ」は試験温度が８℃であったため、無処理であってもポテトチップカラーは低下したが、エチレン処理区での低下程度の方が大きかった。

「きたひめ」は、エチレン処理による影響は小さかった。

「スノーデン」では、処理１週間後にはポテトチップカラーが低下したが、徐々に回復し、3 月には無処理との差は小さくなった。その後、5 月までエチレン処理区と無処理区はほぼ同じ数値であったが、6 月にはエチレン処理区が低下した。

資料　６

有機農産物の日本農林規格

制　　定　平成12年 1月20日農林水産省告示第　59号
一部改正　平成15年11月18日農林水産省告示第1884号
全部改正　平成17年10月27日農林水産省告示第1605号
最終改正　平成21年 8月27日農林水産省告示第1180号

（目的）

第１条　この規格は、有機農産物の生産の方法についての基準等を定めることを目的とする。

（有機農産物の生産の原則）

第２条　有機農産物は、次のいずれかに従い生産することとする。

⑴　農業の自然循環機能の維持増進を図るため、化学的に合成された肥料及び農薬の使用を避けることを基本として、土壌の性質に由来する農地の生産力（きのこ類の生産にあっては農林産物に由来する生産力を含む。）を発揮させるとともに、農業生産に由来する環境への負荷をできる限り低減した栽培管理方法を採用したほ場において生産すること。

⑵　採取場（自生している農産物を採取する場所をいう。以下同じ。）において、採取場の生態系の維持に支障を生じない方法により採取すること。

（定義）

第３条　この規格において、次の表左欄の用語の定義は、それぞれ同表右欄のとおりとする。

用　語	定　　義
有機農産物	次条の基準に従い生産された農産物（飲食料品に限る。）をいう。
使用禁止資材	肥料及び土壌改良資材（別表１に掲げるものを除く。）、農薬（別表２に掲げるものを除く。）及び土壌又は植物に施されるその他の資材（天然物質又は化学的処理を行っていない天然物質に由来するものを除く。）をいう。
組換えＤＮＡ技術	酵素等を用いた切断及び再結合の操作によって、ＤＮＡをつなぎ合わせた組換えＤＮＡ分子を作製し、それを生細胞に移入し、かつ、増殖させる技術をいう。

（生産の方法についての基準）

第４条　有機農産物の生産の方法についての基準は、次のとおりとする。

事　項	基　　準
ほ場又は採取場	１　ほ場については、周辺から使用禁止資材が飛来し、又は流入しないように必要な措置を講じているものであり、かつ、次のいずれかに該当するものであること。 ⑴　多年生の植物から収穫される農産物にあってはその最初の収穫前３年以上、それ以外の農産物にあっては種又は植付け前２年以上（開拓されたほ場又は耕作の目的に供されていなかったほ場であって、２年以上使用禁止資材が使用されていないほ場において新たに農産物の生産を開始した場合にあっては種又は植付け前１年以上）の間、この表ほ場に使用する種子、苗等又は種菌の項、ほ場における肥培管理の項、ほ場における有害動植物の防除の項及び一般管理の項の基準に従い農産物の生産を行っていること。 ⑵　転換期間中のほ場（⑴に規定するほ場への転換を開始したほ場であって、⑴に規定する要件に適合していないものをいう。以下同じ。）については転換開始後最初の収穫前１年以上の間、この表ほ場に使用する種子、苗等又は種菌の項、ほ場における肥培管理の項、ほ場における有害動植物の防除の項及び一般管理の項の基準に従い農産物の生産を行っていること。

	2　採取場については、周辺から使用禁止資材が飛来又は流入しない一定の区域であり、かつ、当該採取場において農産物採取前３年以上の間、使用禁止資材を使用していないものであること。
ほ場に使用する種子、苗等又は種菌	1　この表ほ場又は採取場の項、ほ場における肥培管理の項、ほ場における有害動植物の防除の項、一般管理の項、育苗管理の項及び収穫、輸送、選別、調製、洗浄、貯蔵、包装その他の収穫以後の工程に係る管理の項の基準に適合する種子、苗等（苗、苗木、穂木、台木その他植物体の全部又は一部（種子を除く。）で繁殖の用に供されるものをいう。以下同じ。）又は種菌であること。 2　１の種子、苗等又は種菌の入手が困難な場合は、使用禁止資材を使用することなく生産されたものを、これらの種子、苗等又は種菌の入手が困難な場合は、種子繁殖する品種にあっては種子、栄養繁殖する品種にあっては入手可能な最も若齢な苗等又は天然物質若しくは化学的処理を行っていない天然物質に由来する培養資材を使用して生産された種菌を使用することができる（は種され、又は植え付けられた作期において食用新芽の生産を目的とする場合を除く。）。 3　１及び２に掲げる種子、苗等又は種菌は、組換えＤＮＡ技術を用いて生産されたものでないこと。
ほ場における肥培管理	1　当該ほ場において生産された農産物の残さに由来するたい肥の施用又は当該ほ場若しくはその周辺に生息し、若しくは生育する生物の機能を活用した方法のみによって土壌の性質に由来する農地の生産力の維持増進を図ること。ただし、当該ほ場又はその周辺に生息し、又は生育する生物の機能を活用した方法のみによっては土壌の性質に由来する農地の生産力の維持増進を図ることができない場合にあっては、別表１の肥料及び土壌改良資材（製造工程において化学的に合成された物質が添加されていないもの及びその原材料の生産段階において組換えＤＮＡ技術が用いられていないものに限る。以下同じ。）に限り使用することができる。 2　前項の規定にかかわらず、きのこ類の生産に用いる資材にあっては、次の⑴から⑶までに掲げる基準に適合していること。ただし、たい肥栽培きのこの生産においてこれらの資材の入手が困難な場合にあっては、別表１の肥料及び土壌改良資材に限り使用することができる。 ⑴　樹木に由来する資材については、過去３年以上、周辺から使用禁止資材が飛来せず、又は流入せず、かつ、使用禁止資材が使用されていない一定の区域で伐採され、伐採後に化学物質により処理されていないものであること。 ⑵　樹木に由来する資材以外の資材については、以下に掲げるものに由来するものに限ること。 ア　農産物（この条に規定する生産の方法についての基準に従って栽培されたものに限る。） イ　加工食品（有機加工食品の日本農林規格（平成１７年１０月２７日農林水産省告示第１６０６号）第４条に規定する生産の方法についての基準に従って生産されたものに限る。） ウ　飼料（有機飼料の日本農林規格（平成１７年１０月２７日農林水産省告示第１６０７号）第４条に規定する生産の方法についての基準に従って生産されたものに限る。） エ　有機畜産物の日本農林規格（平成１７年１０月２７日農林水産省告示第１６０８号）第４条に規定する生産の方法についての基準に

	従って飼養された家畜及び家きんの排せつ物に由来するもの ⑶　⑵アに掲げる基準に従ってきのこ類を生産する過程で産出される廃ほだ等については、これらを再利用することにより自然循環機能の維持増進が図られていること。
ほ場における有害動植物の防除	耕種的防除（作目及び品種の選定、作付け時期の調整、その他農作物の栽培管理の一環として通常行われる作業を有害動植物の発生を抑制することを意図して計画的に実施することにより、有害動植物の防除を行うことをいう。）、物理的防除（光、熱、音等を利用する方法又は人力若しくは機械的な方法により有害動植物の防除を行うことをいう。）、生物的防除（病害の原因となる微生物の増殖を抑制する微生物、有害動植物を捕食する動物若しくは有害動植物が忌避する植物若しくは有害動植物の発生を抑制する効果を有する植物の導入又はその生育に適するような環境の整備により有害動植物の防除を行うことをいう。）又はこれらを適切に組み合わせた方法のみにより有害動植物の防除を行うこと。ただし、農産物に重大な損害が生ずる危険が急迫している場合であって、耕種的防除、物理的防除、生物的防除又はこれらを適切に組み合わせた方法のみによってはほ場における有害動植物を効果的に防除することができない場合にあっては、別表２の農薬（組換えＤＮＡ技術を用いて製造されたものを除く。以下同じ。）に限り使用することができる。
一般管理	土壌、植物又はきのこ類に使用禁止資材（古紙に由来する農業用資材（製造工程において化学的に合成された物質が添加されていないものに限る。）及び種子が帯状に封入された農業用資材（コットンリンターに由来する再生繊維を原料とし、製造工程において化学的に合成された物質が添加されていないものに限る。）を除く。）を施さないこと。
育苗管理	育苗を行う場合（ほ場において育苗を行う場合を除く。）にあっては、周辺から使用禁止資材が飛来し、又は流入しないように必要な措置を講じ、その用土として次の１から３までに掲げるものに限り使用するとともに、この表ほ場における肥培管理の項、ほ場における有害動植物の防除の項及び一般管理の項の基準に従い管理を行うこと。 １　この表ほ場又は採取場の項の基準に適合したほ場又は採取場の土壌 ２　過去３年以上の間、周辺から使用禁止資材が飛来又は流入せず、かつ、使用されていない一定の区域で採取され、採取後においても使用禁止資材が使用されていない土壌 ３　別表１の肥料及び土壌改良資材
収穫、輸送、選別、調製、洗浄、貯蔵、包装その他の収穫以後の工程に係る管理	１　この表ほ場又は採取場の項、ほ場に使用する種子、苗等又は種菌の項、ほ場における肥培管理の項、ほ場における有害動植物の防除の項、一般管理の項又は育苗管理の項の基準（以下「ほ場又は採取場の項等の基準」という。）に適合しない農産物が混入しないように管理を行うこと。 ２　有害動植物の防除又は品質の保持改善は、物理的又は生物の機能を利用した方法（組換えＤＮＡ技術を用いて生産された生物を利用した方法を除く。以下同じ。）によること。ただし、物理的又は生物の機能を利用した方法のみによっては効果が不十分な場合には、以下の資材に限り使用することができる。 ⑴　有害動植物の防除目的　別表２の農薬及び有機加工食品の日本農林規格（平成１７年１０月２７日農林水産省告示第１６０６号）別表２の薬剤（ただし、農産物への混入を防止すること。） ⑵　農産物の品質の保持改善目的　別表３の調製用等資材（製造工程において化学的に合成された物質が添加されていないものであって、組

	換えＤＮＡ技術を用いて製造されていないものに限る。） ３　放射線照射を行わないこと。 ４　この表ほ場又は採取場の項等の基準及びこの項１から３までに掲げる基準に従い生産された農産物が農薬、洗浄剤、消毒剤その他の資材により汚染されないように管理を行うこと。

（有機農産物の名称の表示）

第５条　有機農産物の名称の表示は、次の例のいずれかによることとする。

⑴　「有機農産物」

⑵　「有機栽培農産物」

⑶　「有機農産物○○」又は「○○（有機農産物）」

⑷　「有機栽培農産物○○」又は「○○（有機栽培農産物）」

⑸　「有機栽培○○」又は「○○（有機栽培）」

⑹　「有機○○」又は「○○（有機）」

⑺　「オーガニック○○」又は「○○（オーガニック）」

（注）「○○」には、当該農産物の一般的な名称を記載すること。

２　前項の基準にかかわらず、転換期間中のほ場において生産されたものにあっては、前項の例のいずれかにより記載する名称の前又は後に「転換期間中」と記載すること。

３　第１項の基準にかかわらず、採取場において採取された農産物にあっては、同項⑴、⑶、⑹及び⑺の例のいずれかにより記載すること。

別表１

肥料及び土壌改良資材	基　　準
植物及びその残さ由来の資材	
発酵、乾燥又は焼成した排せつ物由来の資材	家畜及び家きんの排せつ物に由来するものであること。
食品工場及び繊維工場からの農畜水産物由来の資材	天然物質又は化学的処理（有機溶剤による油の抽出を除く。）を行っていない天然物質に由来するものであること。
と畜場又は水産加工場からの動物性産品由来の資材	天然物質又は化学的処理を行っていない天然物質に由来するものであること。
発酵した食品廃棄物由来の資材	食品廃棄物以外の物質が混入していないものであること。
バークたい肥	天然物質又は化学的処理を行っていない天然物質に由来するものであること。
グアノ	
乾燥藻及びその粉末	
草木灰	天然物質又は化学的処理を行っていない天然物質に由来するものであること。
炭酸カルシウム	天然物質又は化学的処理を行っていない天然物質に由来するもの（苦土炭酸カルシウムを含む。）であること。
塩化加里	天然鉱石を粉砕又は水洗精製したもの及び天然かん水から回収したものであること。
硫酸加里	天然物質又は化学的処理を行っていない天然物質に由来するものであること。

硫酸加里苦土	天然鉱石を水洗精製したものであること。
天然りん鉱石	カドミウムが五酸化リンに換算して１ｋｇ中９０ｍｇ以下であるものであること。
硫酸苦土	天然物質又は化学的処理を行っていない天然物質に由来するものであること。
水酸化苦土	天然鉱石を粉砕したものであること。
石こう（硫酸カルシウム）	天然物質又は化学的処理を行っていない天然物質に由来するものであること。
硫黄	
生石灰（苦土生石灰を含む。）	天然物質又は化学的処理を行っていない天然物質に由来するものであること。
消石灰	上記生石灰に由来するものであること。
微量要素（マンガン、ほう素、鉄、銅、亜鉛、モリブデン及び塩素）	微量要素の不足により、作物の正常な生育が確保されない場合に使用するものであること。
岩石を粉砕したもの	天然物質又は化学的処理を行っていない天然物質に由来するものであって、含有する有害重金属その他の有害物質により土壌等を汚染するものでないこと。
木炭	天然物質又は化学的処理を行っていない天然物質に由来するものであること。
泥炭	天然物質又は化学的処理を行っていない天然物質に由来するものであること。ただし、土壌改良資材としての使用は、育苗用土としての使用に限ること。
ベントナイト	天然物質又は化学的処理を行っていない天然物質に由来するものであること。
パーライト	天然物質又は化学的処理を行っていない天然物質に由来するものであること。
ゼオライト	天然物質又は化学的処理を行っていない天然物質に由来するものであること。
バーミキュライト	天然物質又は化学的処理を行っていない天然物質に由来するものであること。
けいそう土焼成粒	天然物質又は化学的処理を行っていない天然物質に由来するものであること。
塩基性スラグ	
鉱さいけい酸質肥料	天然物質又は化学的処理を行っていない天然物質に由来するものであること。
よう成りん肥	天然物質又は化学的処理を行っていない天然物質に由来するものであって、カドミウムが五酸化リンに換算して１ｋｇ中９０ｍｇ以下であるものであること。
塩化ナトリウム	海水又は湖水から化学的方法によらず生産されたもの又は採掘されたものであること。
リン酸アルミニウムカルシウム	カドミウムが五酸化リンに換算して１ｋｇ中９０ｍｇ以下であるものであること。
塩化カルシウム	
食酢	
乳酸	植物を原料として発酵させたものであって、育苗用土等のｐＨ調整に使用する場合に限ること。

製糖産業の副産物肥料の造粒材及び固結防止材	天然物質又は化学的処理を行っていない天然物質に由来するものであること。ただし、当該資材によっては肥料の造粒材及び固結防止材を製造することができない場合には、リグニンスルホン酸塩に限り使用することができる。
その他の肥料及び土壌改良資材	植物の栄養に供すること又は土壌改良を目的として土地に施される物（生物を含む。）及び植物の栄養に供することを目的として植物に施される物（生物を含む。）であって、天然物質又は化学的処理を行っていない天然物質に由来するもの（燃焼、焼成、溶融、乾留又はけん化することにより製造されたもの並びに化学的な方法によらずに製造されたものであって、組換えＤＮＡ技術を用いて製造されていないものに限る。）であり、かつ、病害虫の防除効果を有することが明らかなものでないこと。ただし、この資材はこの表に掲げる他の資材によっては土壌の性質に由来する農地の生産力の維持増進を図ることができない場合に限り使用することができる。

別表２

農　　薬	基　　準
除虫菊乳剤及びピレトリン乳剤	除虫菊から抽出したものであって、共力剤としてピペロニルブトキサイドを含まないものに限ること。
なたね油乳剤	
マシン油エアゾル	
マシン油乳剤	
デンプン水和剤	
脂肪酸グリセリド乳剤	
メタアルデヒド粒剤	捕虫器に使用する場合に限ること。
硫黄くん煙剤	
硫黄粉剤	
硫黄・銅水和剤	
水和硫黄剤	
石灰硫黄合剤	
シイタケ菌糸体抽出物液剤	
炭酸水素ナトリウム水溶剤及び重曹	
炭酸水素ナトリウム・銅水和剤	
銅水和剤	
銅粉剤	
硫酸銅	ボルドー剤調製用に使用する場合に限ること。
生石灰	ボルドー剤調製用に使用する場合に限ること。
天敵等生物農薬	
性フェロモン剤	農作物を害する昆虫のフェロモン作用を有する物質を有効成分とするものに限ること。
クロレラ抽出物液剤	
混合生薬抽出物液剤	

ワックス水和剤	
展着剤	カゼイン又はパラフィンを有効成分とするものに限ること。
二酸化炭素くん蒸剤	保管施設で使用する場合に限ること。
ケイソウ土粉剤	保管施設で使用する場合に限ること。
食酢	
燐酸第二鉄粒剤	
炭酸水素カリウム水溶剤	

別表３

調製用等資材	基　　準
炭酸カルシウム	
水酸化カルシウム	
二酸化炭素	
窒素	
エタノール	
カゼイン	
ゼラチン	
活性炭	
タルク	
ベントナイト	
カオリン	
ケイソウ土	
パーライト	
Ｌ－酒石酸	
Ｌ－酒石酸水素カリウム	
Ｌ－酒石酸ナトリウム	
クエン酸	
微生物由来の調製用等資材	
酵素	
卵白アルブミン	
アイシングラス	
植物油脂	
樹皮成分の調製品	
ヘーゼルナッツの殻	
エチレン	バナナ及びキウイフルーツの追熟に使用する場合に限ること。
硫酸アルミニウムカリウム	バナナの房の切り口の黒変防止に使用する場合に限ること。

附　則

（施行期日）

１　この告示は、公布の日から起算して３０日を経過した日から施行する。

（経過措置）

２　この告示の施行の日から起算して１年を経過した日までに行われる有機農産物の格付について

は、この告示による改正前の有機農産物の日本農林規格の規定の例によることができる。

3　この告示の公布の日から起算して３年を経過するまでの間は、この告示による改正後の有機農産物の日本農林規格第４条の表育苗管理の項基準の欄２中「過去３年以上の間、周辺」とあるのは、「周辺」と読み替えて適用する。

4　第４条の表ほ場には種する種子又は植え付ける苗等の項の基準に適合する種子又は苗等の入手が困難な場合は、当分の間、同項の規定にかかわらず、同項の基準に適合する種子又は苗等以外のもの（組換えＤＮＡ技術を用いて生産されたものを除く。）を使用することができる。

附　則（平成１８年１０月２７日農林水産省告示第１４６３号）　抄

（施行期日）

1　この告示は、公布の日から起算して３０日を経過した日から施行する。

（経過措置）

2　この告示による改正後の有機農産物の日本農林規格（以下「新有機農産物規格」という。）別表１に掲げる肥料及び土壌改良資材のうち、植物及びその残さ由来の資材、発酵、乾燥又は焼成した排せつ物由来の資材、食品工場及び繊維工場からの農畜水産物由来の資材並びに発酵した食品廃棄物由来の資材については、新有機農産物規格第４条の表ほ場における肥培管理の項基準の欄１に規定するその原材料の生産段階において組換えＤＮＡ技術が用いられていない資材に該当するものの入手が困難である場合には、当分の間、同項の規定にかかわらず、これらの資材に該当する資材以外のものを使用することができる。

3　新有機農産物規格第４条の表一般管理の項の規定にかかわらず、他に適当な管理方法がない場合には、この告示の公布の日から起算して３年を経過するまでの間は、古紙に由来する農業用資材（製造工程において化学的に合成された物質が添加されていないものに限る。）及び種子が帯状に封入された農業用資材を使用することができる。

4　この告示の公布の日から起算して３年を経過するまでの間は、別表３エチレンの項中「バナナ」とあるのは、「バナナ及びキウイフルーツ」と読み替えるものとする。

附　則（平成２１年８月２７日農林水産省告示第１１８０号）　抄

この告示による改正後の有機農産物の日本農林規格第４条の表育苗管理の項の規定にかかわらず、平成２３年１２月３１日までの間は、たまねぎの育苗用土に粘度調整のためにやむを得ず使用する場合に限り、ポリビニルアルコール、ポリアクリルアミド及び天然物質に由来するもので化学的処理を行ったものを使用することができる。

（最終改正の施行期日）

平成２１年８月２７日農林水産省告示第１１８０号については、平成２１年１０月２７日から施行する。

資料　　7

カナダにおけるエチレン登録の現状
PMRA（農薬管理規制局）による資料
2001 年10月5日

申請規則決定書（案）PRDD2001-04

エチレン（商品名 Eco Sprout Guard）

Pest Management Regulatory Agency
Agence de réglementation de la lutte antiparasitaire

Proposed Regulatory Decision Document PRDD2001-04

Ethylene
Eco Sprout Guard

The active ingredient ethylene, as Eco Sprout Guard technical grade active ingredient (TGAI) and the associated end-use product Eco Sprout Guard EP containing 2–100% ethylene in compressed gas cylinders for the control of sprouting in stored "Russet Burbank" processing potatoes, are proposed for registration under Section 13 of the Pest Control Products Regulations.

This proposed regulatory decision document (PRDD) provides a summary of data reviewed and the rationale for the proposed full registration of these products. The Pest Management Regulatory Agency (PMRA) will accept written comments on this proposal up to 45 days from the date of publication of this document. Please forward all comments to the Publications Coordinator at the address listed below.

(publié aussi en français)

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Foreword

The submissions for registration of Eco Sprout Guard TGAI (ethylene) and its end-use product Eco Sprout Guard EP, supplied by Praxair Inc. and marketed by McCain Foods Limited, have been reviewed by the Pest Management Regulatory Agency (PMRA).

Eco Sprout Guard EP, containing 2–100% ethylene in compressed gas cylinders, was investigated as an alternative product to conventional pesticides for the inhibition of sprouting in stored processing potato tubers. Ethylene occurs ubiquitously in the natural environment and is a natural plant hormone. Ethylene is relatively nontoxic and has a long history of use as a clinical anaesthetic at high concentrations (up to 80–90% in oxygen). At the recommended concentration of 4 ppm, ethylene inhibits excessive sprout growth by reducing apical dominance. Levels of ethylene and its major metabolites in treated potatoes are similar to those in untreated potatoes.

The PMRA has carried out an assessment of available information in accordance with Section 9 of the Pest Control Products (PCP) Regulations and has found it sufficient, pursuant to Section 18.b, to allow a determination of the safety, merit and value of *Eco Sprout Guard TGAI (ethylene) and its end-use product Eco Sprout Guard EP*. The Agency has concluded that the use of *Eco Sprout Guard TGAI (ethylene) and its end-use product Eco Sprout Guard EP* in accordance with the label has merit and value consistent with section 18.c of the PCP Regulations and does not entail an unacceptable risk of harm pursuant to Section 18.d. Therefore, based on the considerations outlined above, the use of *Eco Sprout Guard TGAI (ethylene) and its end-use product Eco Sprout Guard EP* is proposed for full registration, pursuant to Section 13 of the Pest Control Products Regulations.

The PMRA is proposing to grant full registration to this product. The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document to allow interested parties an opportunity to provide input into the proposed registration decision for this product.

Table of Contents

1.0 The active substance, its properties, and uses

1.1 Identity of the active substance and preparation containing it

Active substance		Ethylene
Function		Sprout inhibitor
Chemical name		
1.	International Union of Pure and Applied Chemistry	Ethene
2.	Chemical Abstract Services (CAS)	Ethene
CAS Number		74-85-1
Molecular formula		C_2H_4
Molecular weight		28.06
Structural formula		$CH_2=CH_2$
Nominal purity of active		Pure ethylene gas, 100%
Identity of relevant impurities of toxicological, environmental, and other significance		The product contains carbon monoxide at a maximum level of <0.1%. Impurities of toxicological concern as identified in Section 2.13.4 of DIR98-04 *Chemistry Requirements for the Registration of a Technical Grade of Active Ingredient or an Integrated System Product* or Toxic Substances Management Policy (TSMP) Track-1 materials as identified in Appendix II of DIR99-03 *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy* are not expected to be present or formed in the product.

1.2 Physical and chemical properties of the active substance and end-use product

Technical product: Eco Sprout Guard TGAI

Property	Result	Comment
Colour and physical state	Colourless compressed gas	
Odour	Sweet odour	
Melting point/range	N/A	
Boiling point/range	–103EC	
Specific gravity	0.978 at 0EC (air = 1)	
Vapour density (g/mL)	0.001 26 at 0EC	
Ultraviolet (UV) / visible spectrum	Not expected to absorb UV at wavelengths >300 nm	Photolysis will not be expected
Solubility in water at 20EC	Slightly	
n-Octanol/water partition coefficient (K_{ow})	log K_{ow} = 1.16	Bioaccumulation is not expected
Dissociation constant	Does not dissociate	
Stability (temperature, metal)	The flash point is –136EC. Avoid impact and high temperature at cylinder pressure; incompatible with oxidizing agents, halogens, acid, aluminum chloride and halocarbons	

End-use product: Eco Sprout Guard EP

Property	Result
Colour	Colourless
Odour	Sweet

Property	Result
Physical state	Gas
Formulation type	Compressed gas
Guarantee	2–100%, nominal
Formulants	The product does not contain any EPA List 1 formulants or formulants known to be TSMP Track-1 substances.
Container material and description	Compressed gas cylinders
Oxidizing or reducing action	Incompatible with oxidizing agents, halogens, acids, aluminum chloride and halocarbons
Storage stability	Expected to be stable when stored in the cylinders
Explodability	Spontaneously explosive in sunlight with chlorine. Forms explosive mixture with air and oxidizing agents. Containers may rupture due to heat or fire. Avoid impacts against containers.

1.3 Details of uses

Ethylene is a growth regulator. In potato tubers, ethylene has been documented to shorten the post-harvest rest period, often resulting in earlier sprouting but inhibiting the elongation of sprouts by reducing apical dominance.

Eco Sprout Guard EP, containing from 2 to 100% ethylene in pressurized cylinders, is recommended for application to "Russet Burbank" processing potato tubers in commercial potato storages. Eco Sprout Guard EP is recommended for daily application into the ventilation airstream of the storage facility to attain an ethylene concentration of up to 4 ppm.

2.0 Methods of analysis

2.1 Methods for analysis of the active substance as manufactured

The active was determined using two gas chromatographic (GC) methods.

2.2 Method for formulation analysis

The active was determined using two GC methods.

3.0 Impact on human and animal health

3.1 Integrated toxicological summary

Ethylene is a naturally occurring gaseous chemical produced by all plant tissues in significant amounts and acts as an endogenous plant growth regulator. Ethylene is also a naturally occurring endogenous chemical in humans and laboratory animals and has been identified in the air exhaled by unexposed rats and humans. Possible sources of endogenous ethylene in humans and laboratory animals include lipid peroxidation of unsaturated fats, oxidation of free methionine, oxidation of hemin in haemoglobin and metabolism of intestinal bacteria. In humans, the concentration of ethylene in the blood resulting from its endogenous production is approximately 0.097 nmol/L.

Under environmental conditions, ethylene is a gas; therefore, the most probable route of human exposure to ethylene is by inhalation. Ethylene at high concentrations (up to 80–90% in oxygen) has a long history of use as a clinical anaesthetic, with little concomitant toxicity. Anaesthesia is complete within 20–30 min with 90% in oxygen. Ethylene is more advantageous than ether as an anaesthetic because of safer induction and more rapid recovery. Ethylene has been classified as an asphyxiant in Canada because its presence at high concentrations in air lowers the available oxygen concentration.

The uptake, exhalation and metabolism of ethylene can be described by first-order kinetics. Uptake of ethylene into the body is low due to its low solubility in blood. For rats it is estimated that approximately 15–17% of inhaled ethylene reaches the alveolar blood. In humans, it is estimated that approximately 21% of inhaled ethylene reaches the alveolar blood using a physiological toxicokinetic model which is similar to values obtained for rats. Inhalation of ethylene in human volunteers at atomospheric concentrations of up to 50 ppm by gas uptake in a closed spirometer system indicates that at an alveolar ventilation rate of 150 L/h, approximately 5.6% of inhaled ethylene reaches the alveolar blood with the majority, 94.4%, being exhaled again without becoming systemically available via the blood system. At steady state the estimated alveolar retention in humans is approximately 2–3%. Due to its low blood/gas solubility, ethylene is rapidly excreted and does not appear to accumulate in the body. Ethylene from both endogenous and exogenous sources is metabolized to ethylene oxide in vivo in rats, mice and humans. Studies in healthy volunteers suggest that approximately 2–3% of ethylene absorbed is metabolized to ethylene oxide, whereas up to 98% of ethylene is exhaled unchanged. The data also suggest that the metabolism of ethylene can be stimulated by an inducer of the mixed-function oxidase system.

Ethylene has low acute toxicity via the inhalation route of exposure in mice. There is some acute hazard of dermal and ocular frost burns and of flammability posed by the compressed gas. In a subchronic inhalation study with Sprague-Dawley rats, there were no toxic effects at concentrations up to and including 10 000 ppm, the highest dose tested. In a chronic toxicity/oncogenicity inhalation study with Fischer 344 rats, no significant treatment-related findings or evidence of oncogenicity were observed at ethylene

concentrations up to and including 3000 ppm, the highest dose tested. The weight of evidence suggests that ethylene is not genotoxic. There is inadequate evidence in humans and experimental animals for carcinogenicity of ethylene. Overall, ethylene is not classifiable as to its carcinogenicity to humans (International Agency for Research on Cancer (IARC) classification - Group 3). Ethylene is not listed as a carcinogen by the National Toxicology Program (NTP) or Occupational Safety and Health Association (OSHA).

The toxicological concerns regarding ethylene are related primarily to its metabolites, specifically the initial metabolite, ethylene oxide. Ethylene oxide is a direct alkylating agent that is genotoxic in numerous in vitro and in vivo test systems and is carcinogenic in mice and rats. Positive results have been obtained using the mouse lung tumour bioassay ($70 ppm) and the standard 2-year bioassays in mice and rats at concentrations $100 ppm. Based on these findings, ethylene oxide is classified as carcinogenic to humans by IARC (IARC classification - Group 1) and NTP (*Report on Carcinogens*, 9th edition "known carcinogen"). However, published literature indicates that exposures to 1000 and 40 ppm ethylene in closed inhalation chambers are equivalent to ethylene oxide exposures of 5.6 and 1 ppm, respectively, in rats. When exposure data was combined with previously obtained rat tumour induction data for ethylene oxide, extrapolation of the tumour data to the highest possible ethylene oxide equivalent, 5.6 ppm, indicated that high ethylene exposures would not result in tumour incidence more than 2% above the tumour background level. It was concluded that the body burden of ethylene oxide resulting from such low ethylene oxide exposures (i.e., 5.6 ppm) is too small to lead to a significant increase in tumours in ethylene exposed rats. Published literature also indicates that above concentrations of approximately 1000 ppm ethylene, the V_{max} for ethylene is reached, thus, higher exposures would not yield greater conversion of ethylene to ethylene oxide. Published literature suggest that it would be difficult to obtain statistically significant positive tumour results for ethylene regardless of the dose. In humans, using a physiological model, predicted blood levels resulting from one 8-h exposure to 1 ppm ethylene oxide would be equivalent ethylene oxide levels expected following an 8-h exposure to 45 ppm ethylene assuming bioavailability of 100% for the metabolically formed ethylene oxide (there is some evidence that at low ethylene exposure concentrations the bioavailability of metabolically formed ethylene oxide may be 100%). Based on measurements of haemoglobin adduct levels in humans exposed to up to 5 ppm ethylene, it is estimated that an average of 2–3% of absorbed ethylene is metabolized to ethylene oxide. The current threshold for ethylene oxide of 1 ppm [current OSHA standard for ethylene oxide, i.e., 8-h time-weighted average (TWA) per 40-h work week] is toxicologically equivalent to an ethylene concentration of 37 ppm. Published literature indicates that long-term human occupational exposure to low airborne concentration of ethylene oxide, at or below current occupational exposure limits of 1 ppm (1.83 mg/m^3) would not produce unacceptable increased genotoxic or carcinogenic risk.

Based on these findings and on the proposed conditions of use for ethylene (the ethylene concentration will be a maximum of 4 ppm until the end of the storage period), it is unlikely that ethylene oxide concentrations would reach levels that would produce unacceptable genotoxic or carcinogenic risks.

There is sufficient information from published literature to make a risk assessment for the proposed use of ethylene. Based on information from published literature, ethylene has low toxicity concerns and has been used extensively as an anaesthetic with little concomitant toxicity. Based on the proposed low levels of ethylene exposure, the low absorption rate for ethylene and the low conversion rate of ethylene to ethylene oxide, it is unlikely that ethylene oxide levels would reach unacceptable levels (i.e., >1.0 ppm). It can be concluded that ethylene will be nontoxic to humans under the conditions of use as a plant growth regulator for suppression of sprout growth on stored potatoes, provided that it is used as indicated on the product label; therefore, under the proposed conditions of use as indicated on the product label, it is unlikely that ethylene will present a risk.

3.2 Determination of acceptable daily intake

As indicated by the Health Protection Branch of Health Canada in the "Health and Safety Status Report" for ethylene (May 1994), an acceptable daily intake (ADI) is not required for ethylene, since it is a naturally occurring chemical produced by fruits and vegetables, including potatoes, during senescence. Ethylene is also a naturally occurring endogenous chemical in humans and laboratory animals and has been identified in the air exhaled by unexposed rats and humans. Potential ethylene metabolites have also been shown to occur naturally. Analytical data for these metabolites in treated potatoes showed that residue levels were either nondetectable or were at levels similar to any measurable residues found in controls.

3.3 Acute reference dose

An acute reference dose (ARfD) was not established, since ethylene was considered unlikely to present an acute hazard. The available literature suggests that there are no significant treatment-related findings to indicate a concern in acute dietary risk assessment. The potential risks to humans from exposure to ethylene are considered negligible due to low toxicity concerns and the widespread use of ethylene as an anaesthetic with little concomitant toxicity.

3.4 Toxicology end-point selection—occupational and bystander risk assessment

The primary route of exposure is inhalation. Ethylene has low acute toxicity via the inhalation route. Ethylene is considered a simple asphyxiant. In a subchronic inhalation study from the published literature, there were no toxic effects in Sprague-Dawley rats at concentrations up to and including 10 000 ppm, the highest dose tested. In a published chronic toxicity/oncogenicity inhalation study with Fischer 344 rats, no significant treatment-related findings or evidence of oncogenicity were observed at ethylene

concentrations up to and including 3000 ppm, the highest dose tested. Contact with ethylene as a compressed gas can cause dermal and ocular frost burns and present a hazard due to its flammability. Potential for this type of exposure can be mitigated through labelling. This was considered to be the most appropriate regulatory approach for this active ingredient and a qualitative assessment of exposure and risk for the proposed use of ethylene was conducted.

3.5 Impact on human and animal health arising from exposure to the active substance or to its impurities

3.5.1 Operator exposure assessment

Application to stored potatoes

Eco Sprout Guard consists of compressed ethylene gas contained in pressurized cylinders of varying concentrations (ranging from 2 to 100% ethylene), the balance being made up with nitrogen. Eco Sprout Guard would be applied by releasing the gas in the ventilation system of the potato storage facility at a specific rate up 4 ppm for the duration of the storage period. The proposed label indicates that for best results application must begin at 1–7 days after the potatoes are harvested and continue until 1–7 days before processing. Typically storage operators would have gas cylinders containing concentrations of ethylene to be used. The concentration in the storage facility would be determined by the delivery rate and the percent concentration of ethylene in Eco Sprout Guard. The concentration of ethylene in the storage building would be monitored, continuously and remotely, to ensure that it remains near the target level throughout the storage period. Typically, the ethylene gas delivery system uses programmable controls to operate valves in response to ventilation conditions in the building. The system is self contained and requires human intervention to review and adjust parameters, to connect or disconnect cylinders to replace empty ones or in the event of a leak in the system.

Operator exposure

Potential occupational exposure to ethylene may occur when entering the storage building or its ventilation duct work (e.g., for repair) during application of ethylene or when standing near the ventilation exhaust. The primary route of exposure would be inhalation.

Ethylene is a naturally occurring gaseous chemical produced by both plants and animals. It has had a long history of use as a clinical anaesthetic (anaesthesia is obtained with exposure to concentrations of 80–90% in oxygen) with little concomitant toxicity. It is generally recognized as safe (GRAS) in the U.S. No exposure limits have been established for ethylene by the American Conference of Governmental Industrial Hygienists (ACGIH). The ACGIH classifies ethylene as a “simple asphyxiant.” Respiratory protection is not normally required for simple asphyxiants except in emergency or planned entry into unknown concentration or in areas of oxygen deficiency. In a published subchronic inhalation study with Sprague-Dawley rats, there were no toxic effects at concentrations up to and including 10 000 ppm, the highest dose tested. A 2-year chronic rat inhalation study from the published literature showed no effects in rats

exposed to 3000 ppm ethylene (6 h/day, 5 days/week). Based on this, it is concluded that the potential risk of workers from exposure to ethylene via inhalation, when used under the proposed conditions, is considered negligible.

Potential exposure to high concentrations of ethylene may occur in the event of a leak in an enclosed space. The proposed label includes precautionary statements regarding proper handling of cylinders and gas release system to avoid leaks; as well, the registrant would provide the user with access to information on proper equipment to use for releasing and monitoring ethylene gas. Respiratory protection for entry into an area of unknown ethylene concentration is recommended on the draft label. These precautionary statements are considered adequate.

Handling cylinders of compressed gas or any equipment under pressure represents a hazard due to its flammability and a potential for acute dermal or ocular exposure to the liquefied gas (i.e., it may cause frost burns if in contact with skin or eyes). This risk can be adequately mitigated with use of appropriate protective equipment; long sleeves, long pants, goggles or faceshield and appropriate gloves are considered adequate.

3.5.2 Bystanders

Based on the nature of the proposed use pattern of Eco Sprout Guard, there would be negligible potential for exposure of bystanders.

3.5.3 Workers

Workers may enter a storage area (e.g., for potato inspection) during or after treatment with ethylene before ventilation is complete (see section 3.5.1 for an assessment of worker potential exposure).

4.0 Residues

No residue data were submitted with this petition. However, previously submitted data and information in support of a former petition to register use of ethylene as a potato sprout inhibitor were summarized by the Health Protection Branch of Health Canada in May 1994 in the "Health and Safety Status Report" for ethylene. Information excerpted from this report is presented in this chapter.

Data provided indicate that the metabolism of ethylene, while not specifically elucidated in potatoes, is similar and probably identical to those metabolic pathways determined for ethylene metabolism in many plants. Potato tubers, as senescent tissues, exhibit low basal metabolic rates such that ethylene is metabolized very slowly, if at all. Endogenous concentrations of ethylene range between 0.0007–0.15 ppm for nonsprouting tubers and 0.1–3 ppm for sprouted tubers. These low concentrations of ethylene, combined with the low diffusion rates suggest that low concentrations of ethylene metabolites would be expected in stored tubers.

Ethylene and its potential metabolites were not identified in treated potatoes at levels exceeding those found in control potatoes, and therefore, animal metabolism and livestock feeding studies were not considered necessary for evaluation.

Residue data was provided for potatoes treated with 4 ppm ethylene for up to 150 days of storage. Residues of chloroethanol, dichloroethane, bromoethanol, ethylene oxide, and ethylene glycol (including its glucoside) residues were in total less than 0.1 ppm. Residues for the metabolite of greatest toxicological concern, ethylene oxide, were <2 ppm (the lower limit of quantitation (LLQ) of the analytical method employed). In addition, the processing or cooking of tubers is expected to result in a reduction of volatile residues (ethylene oxide) by up to 90%. This dissipation of residues would occur by diffusion out of potato tissues during processing of the tubers and by heat-assisted volatilization during cooking.

The partition coefficient for ethylene into potato tuber tissue is very low (0.207), indicating that there is little if any metabolism, compartmentalization of ^{14}C-ethylene by potato tubers or both. Typical soil atmospheres contain about 10 ppm endogenous ethylene levels that can increase as the moisture status of the soil increases. This indicates that developing potato tubers, which are metabolically active, might be expected to metabolize and bioaccumulate ethylene residues. This level of background exposure is 2.5 times greater than that proposed for supplementation of ambient storage bin atmospheres. No residues of ethylene metabolites (after correction for some measurable residues of ethylene glycol and its glucoside) were determined above LLQs in mature tubers for any treated potato tubers in the 1993 and 1994 research trial residue studies.

Evidence was presented that elucidated the impermeability of ethylene into potato tubers. Potato tubers have a high resistance to diffusion because the periderm of the tuber presents a barrier to gaseous diffusion and the bulk of the diffusion occurs through a very small area of the tuber, up to 2% of its volume. This condition effectively blocks movement of exogenous ethylene into the tuber (even against a concentration gradient) thereby maintaining internal concentrations of ethylene in the tuber at endogenous levels.

Processing studies were not performed for ethylene-treated potatoes. However, the processing of treated tubers into french fries, powdered potatoes, potato flour or cooking of raw potato tubers would reduce the residue of most concern, ethylene oxide, if it were present at levels above background. Ethylene oxide is a gas at room temperature and a liquid below 12EC. It would be expected to volatilize out of potatoes during cooking.

Based on the data submitted, residues in potatoes treated according to the proposed label directions will not result in residues of ethylene or its probable major metabolites above levels found in untreated potatoes. Therefore, no dietary risk assessment is considered necessary, and no MRLs are proposed.

5.0 Fate and behaviour in the environment

5.1 Physical and chemical properties relevant to the environment

The physicochemical properties of ethylene, summarized in Table 5.1, are based on a review conducted by the Laboratory Services Subdivision and other information gathered from various sources. Active ingredient purity was >98.5% in the reviewed studies.

Table 5.1 Physical and chemical properties relevant to the environment

Property	Value	Comments
Water solubility	22.6 mL/100 mL at 0EC; 12.2 mL/100 mL at 20EC	Sparingly soluble
Vapour pressure	4100 kPa at 0EC; 1063 kPa at 50EC	Product is a gas
log K_{ow} (25EC)	1.16	Bioaccumulation is not expected
Dissociation constant (pKa at 20EC)	Not applicable	No dissociable groups present in the active ingredient (a.i.)
UV / visible spectrum	Not expected to absorb UV at wavelength >300 nm	Photolysis is not expected to be route of dissipation in the environment

Summary of environmental chemistry and fate studies

No data were submitted or requested on the environmental fate of ethylene because this gas occurs naturally in the environment and the contribution from the proposed use will not be significant.

Expected environmental concentrations

Ethylene use in storage will only impact the expected environmental concentrations (EEC) of ethylene in the atmosphere; however, the contribution of ethylene from the proposed use site to atmospheric concentrations is considered to be negligible.

It is estimated that 89% of natural and anthropogenically produced ethylene gas is destroyed in the troposphere by OH^- radicals, and 8% is destroyed in reactions with ozone. Approximately 3% is transported into the stratosphere. Estimated lifetime in the atmosphere is approximately 2–4 days.

6.0 Effects on non-target species

No data were submitted or requested on effects to nontarget organisms because the contributions from the proposed use will not be significant. Adverse effects on nontarget organisms from the proposed use of ethylene, therefore, are not expected.

7.0 Efficacy

7.1 Effectiveness

7.1.1 Intended use

Eco Sprout Guard EP is intended for use on "Russet Burbank" potatoes in commercial storage facilities to inhibit sprout growth.

7.1.2 Mode of action

Ethylene is a plant growth regulator. In potatoes, ethylene has been documented to shorten the post-harvest rest period, resulting in earlier sprouting but inhibiting the elongation of sprouts by reducing apical dominance. Ethylene also enhances the abscission of sprouts.

7.1.3 Crops

Eco Sprout Guard EP is intended for use on stored "Russet Burbank" potatoes for processing.

7.1.4 Effectiveness against sprouting

Laboratory and commercial scale trials were conducted in which the efficacy of Eco Sprout Guard EP was assessed for the inhibition of sprouting in "Russet Burbank" processing potato tubers. In laboratory trials conducted from 1991–1992 to 1995–1996, Eco Sprout Guard EP was applied to tubers in barrels or steel cabinets to abruptly raise the concentration to 4 ppm once tubers had been permitted to cure (suberize) and cool to the final storage temperature of 9EC, about 8 weeks after the beginning of storage. A commercial standard treatment of chlorpropham (CIPC) was applied to tubers (dipped in 1% emulsion) in each trial.

No sprouting was observed in the CIPC treatment. In the ethylene treatment, the weight of large sprouts (>5 mm) was minimal or absent and ranged from 0 to 0.01 and from 0 to 0.5 g kg^{-1} tuber fresh weight at 20 and 25 weeks after the initiation of application, respectively. In contrast, large sprout weight in the untreated control at 20 and 25 weeks ranged from 2.2 to 17.4, and from 8.5 to 38.5 g kg^{-1} tuber fresh weight, respectively.

Sprout length increased over time but was always less for ethylene-treated tubers than untreated control tubers. Sprout length averaged 9 mm after 25 weeks of ethylene treatment whereas that in the untreated control averaged 204 mm.

Ethylene often increased number of small sprouts (2–5 mm) relative to the untreated control. At the biochemical and cellular level, continual ethylene exposure may have terminated rest (dormancy) in tuber eyes, possibly leading to an increase in sprout initiation while preventing excessive growth of these sprouts through the inhibition of cell differentiation and elongation. The force required to remove sprouts on ethylene treated potatoes was quantitatively assessed in the 1993–1994 trial and was determined to be significantly less than on untreated tubers.

In a laboratory trial conducted in 1997–1998, ethylene applied in accordance with the proposed application method resulted in sprouts that were less than 5 mm long at 33 weeks after the beginning of treatment. No sprouting was observed in the CIPC control treatment.

In commercial-scale trials conducted from 1992–1993 to 1994–1995, ethylene was applied to potato tubers to abruptly raise the ethylene concentration in the storage building to 4 ppm once tubers had been permitted to cure and cool to the final storage temperature of 9EC. In each trial, a commercial standard treatment of CIPC was applied once to cured tubers in a neighbouring storage building as an aerosol (Stanchem Sprout Nip 840). Ethylene reduced sprout number, sprout weight and sprout length. In 1992–1993, the longest sprout observed after 4 months of ethylene treatment was 2 mm, and total sprout weight averaged less than 0.01 g per tuber. No sprouting was observed in the CIPC treatment in this trial. In the trial conducted in 1993–1994, ethylene-treated tubers had higher sprout weight and sprout number than CIPC-treated tubers up until 22 weeks of storage. After this time, CIPC-treated tubers had large increases in sprout length and weight, such that by week 29, CIPC-treated tubers had about five times the sprout weight that ethylene-treated tubers had. CIPC residues are known to gradually decline over time, such that retreatment is often required to maintain sprout inhibition following 4–6 months of storage. In 1994–1995, it was stated in the trial report that a similar degree of sprout control was achieved with ethylene as in the previous 2 years and that sprout control was less than that achieved with CIPC. In the latter two trials, some sprouting was observed in CIPC treatment along the wall of the storage building, where it was likely CIPC did not reach the tubers. Ethylene is a lighter gas than CIPC applied as an aerosol, and therefore, ethylene is distributed more evenly throughout the storage pile than CIPC. The percentage of tubers with internal sprouts was lower for the ethylene treatment (0.01–0.05%) than for the CIPC treatment (0.5–0.7%).

In an additional commercial-scale trial conducted in 1998–1999, the degree of sprout inhibition was observed to be greater for the treatment of ethylene, applied in accordance with the proposed method, than for the CIPC treatment after 6 months of storage probably due to decreasing CIPC residues on tubers. At 6 months after the beginning of storage, about 17 and 48% of tubers treated with ethylene and CIPC had at least one sprout,

respectively. By the final removal at 8 months, 37 and 56% of tubers treated with ethylene and CIPC, respectively, had at least one sprout. After 6 months of ethylene treatment, weight of small and large sprouts each averaged less than 1 g in tuber samples of approximately 35 kg, whereas the weight of small and large sprouts in CIPC-treated tubers averaged 3 and 7 g in similar-sized samples. After 8 months of ethylene treatment, the mean weight of small and large sprouts was about 17 and 42 g per 35 kg sample, respectively, whereas the mean weight of small and large sprouts of tubers treated with CIPC averaged 16 and 167 g, respectively. The mean maximum sprout length observed in ethylene-treated tubers was 6.5 and 27.5 mm at 6 and 8 months of storage, respectively, much shorter than the 45 and 122 mm observed for the CIPC treatment at these two evaluation times.

In each of the commercial trials, sprouts of ethylene-treated tubers were typically stunted, often branched and very brittle, such that these club-shaped sprouts easily fell off when the tubers were removed from storage.

7.2 Undesirable or unintended side effects on treated plant products

Potato tuber fry colour, as measured on an Agtron reflectance colorimeter (range of 0 = black to 100 = white), was assessed in the same laboratory trials in which efficacy was evaluated. In trials conducted from 1991–1992 to 1995–1996, fry colour generally improved (higher Agtron scale value) with storage time for all treatments. Tubers treated daily with 4 ppm ethylene were usually darker upon frying than either the untreated control or the CIPC treatment, which was related to higher reducing sugar levels in ethylene-treated tubers. At the 25-week evaluation date, relative fry colour among treatments was variable over years. Fry colour of ethylene-treated tubers was darker than untreated control tubers in two trials and darker than CIPC-treated tubers in three trials, was similar to that of CIPC-treated tubers in one trial and was lighter than CIPC-treated tubers in one trial. When averaged over the 5 years, ethylene-treated tubers had a lower Agtron value (by 7–10 points) than CIPC-treated tubers when assessed from 5 to 25 weeks. In the trial conducted in 1997–1998, ethylene was applied in accordance with the proposed application method to attain a maximum ethylene concentration of 4 ppm in the storage facility. The treatment evaluated in earlier trials was included for comparison along with a CIPC control. Fry colour of tubers treated with ethylene according to the proposed application method was 6–7 Agtron units darker than CIPC-treated potatoes from 18 to 33 weeks after the beginning of storage. In contrast, potato tubers treated with ethylene beginning at the end of the cooling period resulted in fry colour that was 19–25 Agtron units darker than that treated with CIPC. In an additional trial conducted in 1996–1997, ethylene applied in accordance with the proposed application method resulted in fry colour that was 15–22 Agtron units higher (lighter) than where ethylene had been applied at the end of the cooling period.

Fry colour was assessed in the same commercial-scale trials in which efficacy was evaluated. Fry colour of potato tubers randomly selected from the storage pile was assessed weekly in each of the trials conducted in 1992–1993, 1993–1994 and

1994–1995. Fry colour was generally darker in ethylene-treated tubers than in CIPC-treated tubers in all 3 years, regardless of when data were collected. Unlike the laboratory trials conducted from 1991–1992 until 1995–1996, fry colour did not improve over storage time for either of these treatments. Over the 26 weeks following the initiation of ethylene treatment, U.S. Department of Agriculture fry colour grade ratings (range of 1=light to 7=dark) for ethylene- and CIPC-treated tubers were 3.0 and 2.6 in 1992–1993, 3.4 and 2.8 in 1993–1994, and 2.5 and 1.7 in 1994–1995, respectively.

In the commercial-scale trial conducted in 1998–1999, potato tubers treated with ethylene applied in accordance with the proposed application method resulted in darker fry colour than CIPC after 3 and 6 months of storage. After 3 and 6 months of storage, the fry colour of tubers treated with ethylene were, respectively, 5 and 6 Agtron points lower on average than tubers treated with CIPC. Fry colour of ethylene-treated tubers and CIPC-treated tubers were similar after 8 months of storage.

7.3 Observations on undesirable or unintended side effects

Eco Sprout Guard EP is proposed for post-harvest use only on stored "Russet Burbank" potato tubers for processing in closed-system commercial storage facilities. It would not be expected to impact other crops. It would not be used on or near seed potatoes.

7.4 Economics

In 1998–1999, 4 292 000 t of potatoes were produced in Canada on 156 000 ha. Since 1992–1993, potato production has increased by 2–3% per year. In 1998, 620 000 t of potatoes were exported, mainly to the U.S. In that year, 30% of fresh exports were seed potatoes, and 70% were table stock potatoes and potatoes for processing. Approximately 50% of all potatoes grown in Canada are processed, much of which is exported as frozen french fries. In 1998, 483 436 t of frozen french fries valued at $461 million were exported, mainly to the U.S., but also to more than 90 countries worldwide. Between 1995 and 1998, the quantity and value of exported frozen french fries more than doubled. The importance of processed potato products to the Canadian economy is expected to continue to increase.

7.5 Sustainability

7.5.1 Survey of alternatives

7.5.1.1 Nonchemical control practices

Storage at very low temperatures (3 or 4EC) may be used to delay sprouting of potato tubers; however, these temperatures may induce high levels of reducing sugars, thereby resulting in fry colour of the processed product that is too dark to command top grades and prices.

7.5.1.2 Chemical control practices

Products containing maleic hydrazide or chlorpropham, listed in Table 7.5, are registered for control of sprouting in potatoes. There are two types of chlorpropham products: those that are applied as aerosols in the ventilation system of the potato storage building and those that are applied as emulsions to potatoes in the packing line. Products of the latter type are not typically used for processing potatoes and are not shown in Table 7.5.

Table 7.5 Alternative products for control of sprouting of stored processing potatoes

Active ingredient	End-use products	Mode of action	Application timing	Application rate
Maleic hydrazide	Royal MH 60SG (Reg. No. 18143)	Inhibits cell division	Applied in the field between 2–3 weeks past full bloom and 2 weeks before expected date of topkill or first frost, and when tubers are at least 4–5 cm in diameter	3.4 kg a.i./ha
Chlorpropham	Sprout Nip 840 (Reg. No. 18833)	Inhibits cell division	After harvesting, potatoes are allowed to cure (suberize) for at least 2 weeks before application	Sufficient product applied to achieve deposit of 6–12 ppm on potatoes
	Decco 273 Aerosol Potato Sprout Inhibitor (Reg. No. 24007)			For <4 months storage: 1 kg a.i./60 t potatoes; For 4–6 months storage: 2 kg a.i./50 t potatoes
	Clean Crop Spud-Nic Aerosol Grade (Reg. No. 24691)			For 3 months storage: 1.5–2 kg a.i./100 t potatoes; For 4–6 months storage: 3–3.75 kg a.i./100 t potatoes
	Ag-Services Potato Sprout Inhibitor (Fogging Grade) (Reg. No. 11848)			For 3 months storage: 1.5–2 kg a.i./100 t potatoes; For 4–6 months storage: 3–3.75 kg a.i./100 t potatoes
	Ag-Services 750A Potato Sprout Inhibitor (Fogging Grade) (Reg. No. 25834)			For 3 months storage: 1.5–2 kg a.i./100 t potatoes; For 4–6 months storage: 3–3.75 kg a.i./100 t potatoes

7.6 Conclusions

7.6.1 Summary

Data generated in laboratory and commercial-scale trials demonstrated that Eco Sprout Guard EP, when applied in accordance with the proposed method, can be expected to effectively inhibit sprouting of stored "Russet Burbank" processing potatoes while having minimal impact on processed product quality, such as fry colour. The accepted uses summarized in Table 7.6 are based on the value assessment.

Table 7.6 Summary of accepted use for Eco Sprout Guard EP

Crop	Potatoes (*Solanum tuberosum*)
Cultivar	Russet Burbank (for processing only)
Application timing	Throughout the storage period (up to 10 months)
Frequency of application	Daily during ventilation cycles
Application method	Applied from a pressurized gas cylinder into the ventilation airstream of the storage building to attain an ethylene concentration of up to 4 ppm.
Pest controlled	Sprouting

8.0 Toxic Substances Management Policy

Ethylene occurs naturally in the environment. The contribution from this use will not be significant. The technical grade ethylene does not contain any impurities or microcontaminants known to be Toxic Substances Management Policy (TSMP) Track-1 substances. The end-use product, Eco Sprout Guard EP does not contain any U.S. Environmental Protection Agency List 1 formulants or formulants known to be TSMP Track-1 substances.

9.0 Proposed regulatory decision

The Pest Management Regulatory Agency (PMRA) has carried out an assessment of available information in accordance with Section 9 of the Pest Control Products (PCP) Regulations and has found it sufficient, pursuant to Section 18.b, to allow a determination of the safety, merit, and value of Eco Sprout Guard TGAI and Eco Sprout Guard EP, proposed for registration by McCain Foods Ltd. The PMRA has concluded that the use of Eco Sprout Guard TGAI and Eco Sprout Guard EP in accordance with the label has merit and value consistent with Section 18.c of the PCP Regulations and does not entail an unacceptable risk of harm pursuant to Section 18.d. Therefore, based on the considerations outlined above, the use of Eco Sprout Guard TGAI and Eco Sprout Guard EP for the control of sprouting on stored "Russet Burbank" potatoes for processing is proposed for full registration, pursuant to Section 13 of the PCP Regulations.

The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document to allow interested parties an opportunity to provide input into the proposed registration decision for this product.

List of abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists
a.i.	active ingredient
ADI	acceptable daily intake
ARfD	acute reference dose
bw	body weight
CIPC	chlorpropham
d	day(s)
DNA	deoxyribonucleic acid
EEC	expected environmental concentration
EP	end-use product
EPA	U.S. Environmental Protection Agency
g	gram(s)
GC	gas chromatography
GRAS	generally recognized as safe
h	hour(s)
ha	hectare(s)
IARC	International Agency for Research on Cancer
K_{ow}	*n*-octanol/water partition coefficient
kg	kilogram(s)
kPa	kilo-Pascal(s)
L	litre(s)
LLQ	lower limit of quantitation
m	metre(s)
mL	millilitre(s)
mm	millimetre(s)
nm	nanometre(s)
nmol	nanomoles(s)
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PMRA	Pest Management Regulatory Agency
PRDD	proposed regulatory decision document
ppm	parts per million
t	tonnes
TGAI	technical grade active ingredient
TS	test substance
TSMP	Toxic Substances Management Policy
TWA	time-weighted average
UV	ultraviolet
FL	microlitre

Pest Management Regulatory Agency
Agence de réglementation de la lutte antiparasitaire

Regulatory Decision Document RDD2001-07

Ethylene
Eco Sprout Guard

The active ingredient ethylene, as Eco Sprout Guard TGAI, and the associated end-use product Eco Sprout Guard EP containing 2–100% ethylene in compressed gas cylinders for the control of sprouting in stored "Russet Burbank" processing potatoes, are eligible for full registration under Section 13 of the Pest Control Products Regulations.

This Decision Document outlines this stage of the Pest Management Regulatory Agency's regulatory decision-making process concerning the use of ethylene and the end-use product Eco Sprout Guard EP for the control of sprouting in stored "Russet Burbank" processing potatoes.

(publié aussi en français) **December 28, 2001**

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1.0 Introduction

This Decision Document outlines the Pest Management Regulatory Agency's (PMRA) regulatory decision-making process concerning the use of Eco Sprout Guard EP containing ethylene, for the control of sprouting in stored "Russet Burbank" processing potatoes.

2.0 Background

The PMRA carried out an assessment of available information in accordance with Section 9 of the Pest Control Products (PCP) Regulations. The assessment found that there was sufficient information, pursuant to Section 18.b, to allow a determination of the safety, merit, and value of ethylene and the end-use product Eco Sprout Guard EP marketed by McCain Foods Ltd. The PMRA concluded that the use of Eco Sprout Guard EP in accordance with the label accompanying the product has merit and value consistent with Section 18.c of the PCP Regulations and does not entail an unacceptable risk of harm under Section 18.d.

These products were proposed for registration in Proposed Regulatory Decision Document PRDD2001-04. No comments were received by the PMRA concerning PRDD2001-04.

3.0 Regulatory Decision

Based on the considerations outlined above, ethylene and the associated end-use product Eco Sprout Guard EP, for the control of sprouting in stored "Russet Burbank" processing potatoes, are eligible for full registration, pursuant to Section 13 of the PCP Regulations.

（参考資料） カナダにおけるエチレン登録の現状

PMRA（農薬管理規制局)による資料

2001 年10月5日

申請規則決定書（案）PRDD2001-04

エチレン（商品名 Eco Sprout Guard）

活性物質エチレン、Eco Sprout Guard TGAI および Eco Sprout Guard EP（2-100%圧縮ガスシリンダー）は、加工用貯蔵”Russet Burbank”ジャガイモの萌芽抑制に使用するために、PCP 規則の第 13 条のもとに登録が提案される。

登録申請書には、データの要約とこの製品の完全登録のための理論的根拠が示されている。PMRA(農薬管理規制局)は、この書類の提出日付から45日以内にこの提案について文書でコメントする予定である。下記に示した住所に Publications Coordinators に対して意見を期待している。

はじめに

PMRA（農薬管理規制局)は、Eco Sprout Guard TGAI（エチレン)とその商品 Eco Sprout Guard EP（Praxian 会社によって製造、McCain Foods 会社によって販売）の登録出願書を審査する。

Eco Sprout Guard EP は、2-100%圧縮ガスシリンダー状容器、加工用貯蔵ジャガイモでの萌芽抑制のための代替農薬として実験された。エチレンは、自然環境ではどこにでも存在する自然植物ホルモンである。エチレンは毒性がなく、高濃度（大気中 80-90%）では臨床用の麻酔剤として使用された歴史がある。4ppm の濃度のエチレンは、頂芽優性を抑えることによりジャガイモ塊茎の萌芽を抑制する。エチレンを処理したジャガイモのエチレンレベルとその主要代謝産物は、無処理のものと同じである。

PMRI は、PCP Regulations(害虫駆除製剤規則)の第9条の規定に従って提出案件の評価を行い、第18.b 条によって Eco Sprout Guard TGAI（エチレン)およびその最終商品 Eco Sprout Guard EP の安全性、利点、価値について決定を下した。当局は、表示に基づいた Eco Sprout Guard TGAI（エチレン)およびその最終商品 Eco Sprout Guard の使用が、PCP 規則の第 18.c 条に合致してメリットと価値があり、第 18d 条によって危害の認容できない危険性も引き起こさないと結論した。それ故に、上記に概略した事項に基づき、Eco Sprout Guard TGAI（エチレン）およびその最終産物 Eco Sprout Guard EP の使用について、PCP 規則の第 13 条によって完全登録を提案する。

PMRA は、この商品の完全登録を取得するための提案を行っている。この製品が提案された規則決定に関係機関が加わるための機会を与えるために、PMRA は、この提出日付から45日以内に この申請書について文書によってコメントを受理する予定である。

目　　次

1 活性物質、特性および使用

1.1 活性物質の同定とそれを含む製剤

活性物質:エチレン

機能:萌芽抑制

化学名:

1、 国際純正応用化学連合、エチレン

2、 化学情報検索サービス機関 (CAS)、エチレン

CAS 番号:74-85-1

分子式:C_2H_4

分子量:28.06

構造式:CH_2=CH_2

純度:純粋エチレンガス、100%

毒性、環境、その他意味のある関連不純物の同定:製品は最大 0.1%以下の1酸化炭素を含む。毒性関蓮不純物は、下記に示す。(省略)

1.2 活性物質の物理化学的性質と最終用途製品

工業製品:Eco Sprout Guard TGAI

特性	結果	コメント
色と物理的状況	無色で圧縮ガス	
匂い	甘い	
融点／範囲	なし	
沸点／範囲	マイナス 103 C	
比重	0.978 (0 C)(大気＝1)	
蒸気密度 (g/mL)	0.00126 (0 C)	
紫外線／可視スペクトル	波長＞300nm, UV 吸収なし	光分解は可能性がない
溶解性(20C)	わずか	
オクタノール/水分配係数(K_{OW})	logK_{OW}=1.16	生物濃縮は可能性がない
解離定数	解離しない	
安定性(温度、金属)	引火点はマイナス 136 C 圧縮状態では衝撃と高温はさける;酸化物、ハロゲン、酸、塩化アルミニウムおよびハロカーボンとは不親和性である	

最終用途製品:Eco Sprout Guard EP

特性	結果
色	無色
匂い	甘い
物理的状態	ガス
製剤のタイプ	圧縮ガス
保証	2-100%, 公称
製剤	生産物はどのような EPA List 1 製剤や TSMP-1 物質として知られている製剤も含まない。
容器材料と表示	圧縮ガスシリンダー容器
酸化および還元作用	酸化物、ハロゲン、酸、塩化アルミニウムおよびハロカーボンとは不親和性である
貯蔵安定性	シリンダー状容器で貯蔵する場合は安定である。
爆発性	自然では塩素を含む日光のもとでは爆発性である。大気と酸化剤と爆発性混合の型になっている。熱を火災によって容器が破裂することがある。容器に対する衝撃を防ぐこと。

1.2 使用詳細

エチレンは成長調節剤である。ジャガイモ塊茎では、エチレンは収穫後の休眠期間を短縮させ、時に早期萌芽を生じるが、しかし頂芽優性を抑制することによって萌芽伸長を阻害する。

Eco Sprout Guard EP は、2-100%エチレンの圧縮円筒型容器に充填され、貯蔵中の加工用ジャガイモ”Russet Burbank”の使用に適用される。Eco Sprout Guard EP は、4ppm のエチレン濃度に調節できる貯蔵施設の循環換気システムに連続処理される。

2 分析方法

2.1 工場における活性物質の分析方法

活性は、2種のガスグロマトグラフィー法によって測定された。

2.2 製剤の分析方法

活性は2種のガスグロマトグラフィー法によって測定された。

3 ヒトと動物に対する影響

3.1 総合的な毒性についての要約

エチレンは、すべての植物組織から生産されるガス状の化学物質として自然に存在し、植物成長調節作用として機能する。エチレンはまたヒトおよび家畜の内生の化学物質として自然に存在し、未暴露のラットやヒトによって吐き出された大気中からも検出される。ヒトや家畜のもつ内生エチレンの発生源は、不飽和脂肪の過酸化、フリーのメチオニンの酸化、ヘモグロビンのヘミンの酸化および腸内細菌の代謝などが考えられる。ヒトでは、内生生産から生じる血液中のエチレン濃度は、約 0.097 nmol/L である。

環境条件のもとでは、エチレンはガス状である。そのためエチレンによるヒトへの汚染のルートは吸入による。高濃度のエチレン(酸素中 80-90%まで)は、臨床的な麻酔剤として使用された歴史的な経緯があるが、ほとんど合併毒性はないとされている。酸素中に 90%エチレンが含まれると、20-30 分以内に完全に麻酔がかかる。麻酔剤としてのエチレンは、吸入に安全性が高く、回復性が早いことから、エーテルより利点が多いとされている。エチレンはカナダでは、大気中に高濃度で存在すると酸素濃度を低下させるため窒息剤として分類されている。

エチレンの摂取、発散および代謝は、一時速度式によって表現することができる。体内へのエチレンの摂取は、血液中では低溶解性のために低い。ラットでは、摂取されたエチレンの 15-17%が肺胞血液に達すると算出されている。ヒトでは、21%のエチレンが肺胞血液に達する(生理的毒性カイネテックシステムを用いて)。密閉条件では、50 ppm の濃度のエチレンをヒトの体内に取り込ませると、150L/H の割合で約 5.6%のエチレンが肺胞血液中に達し、94.4%が血液システムを通じて全身に利用されずに排出される。定常状態では、ヒトで算出された肺胞保持割合は、約 2-3%である。血液中ではガス溶解性が低いため、エチレンは敏速に排泄され、体内には蓄積されない。内部また外部から供給されたエチレンは、ラット、マウス、ヒトにおいても生体内で酸化エチレンに代謝される。健全なヒトでの実験から、吸収された約 2-3%のエチレンは酸化エチレンに代謝されるが、それに対して 98%のエチレンは変化せず放出される。またエチレンの代謝は混合機能オキシダーゼ系の誘導因子によって活性化されるというデータもある。

マウスを用いた暴露実験から、エチレンは低急性毒性であるとされている。圧縮ガスに接触すると、皮膚、目の霜、やけどなどいくつかの急性的な危険がある。Sprague-Dawley ラットを用いた摂取実験では、10000 ppm 摂取(試験中最高濃度)でも毒性の影響は認められなかった。Fischer 344 ラットを用いた慢性毒性／発がん性吸入実験では、エチレン濃度 3000 ppm(試験中の最高濃度)でも、処理区における有意な違いや発がん性の証拠は観察されなかった。重要な証拠はエチレンが遺伝毒性でないことである。ヒトと動物実験からエチレンは発がん性がないとされている。総括すると、エチレンは、ヒトに対する発がん性としては分類されていない(IARC 国際癌研究機関の分類、グループ3)。エチレンは、NTP(国家毒性プログラム)および OSHA (職業安全衛生管理局)でも発がん物質としてリストされていない。

エチレンの毒性について重要なことは、基本的にはその代謝産物、特に初期代謝産物である酸化エチレンとの関係である。酸化エチレンは直接アルキル化剤である。それは多くの生体内、生体外実験例から遺伝毒性があり、マウスやラットに発がん性があるとされている。マウス肺がん生物検定（70ppm）と標準2年間マウスとラット生物検定（100ppm 濃度）から陽性の結果を得ている。これらの実験に基づき、IARC(IRAC 分類、グループ1)とNTP(発ガン物質報告，9版、“既知の発がん物質“)は、酸化エチレンがヒトに対して発がん性であると分類している。 しかしながら、文献上では、ラットを用いた密閉容器内吸入実験、1000 および 40ppm エチレンの暴露は、それぞれ 5.6 および1ppm の酸化エチレンに匹敵する。この暴露結果をすでに得られた酸化エチレンに対するラットガン誘因結果と加味して考えると、酸化エチレンが発がん性を示す推定値、5.6 ppm は、発ガン発生率2%を超えるレベルに至っていない。そのような低い酸化エチレン暴露（5.6ppm）から生じる酸化エチレンの身体負荷量(体内蓄積物)は、エチレンを暴露したラットにおいて発ガン性を誘因するにはあまりにも低すぎると結論された。また、文献上では、約 1000ppm のエチレン濃度は、すでにエチレンの Vmax に達している。すなわち、より高い濃度のエチレン暴露は、必ずしも高濃度の酸化エチレンへの変換を伴っていないことを意味している。文献によると、エチレンの濃度に関わらず、統計的に有意な発がん性を示す数値を得るのは困難である。生理的モデルを用いたヒト実験では、1 ppm 酸化エチレンを8時間暴露で生じる予測血液レベルは、45 ppm エチレンを8時間暴露後に生じる予測レベルと同等であることが示された。5 ppm エチレンを暴露したヒトにおけるヘモグロビン付加物レベルの測定から、吸収されたエチレンの平均 2-3%は、酸化エチレンに代謝されると算出されている。最新の基準（酸化エチレンの最新 OSHA 基準、週 40 時間就業、8時間加重平均）によると、1 ppm の酸化エチレンは毒性的には 37 ppm のエチレン濃度と同等である。文献上、酸化エチレンの低大気濃度での長時間職業上の暴露は、その限界濃度は 1ppm (1.83 mg/m^3)かそれ以下では、遺伝毒性や発がん性の危険はないとされている。

これらの事実およびエチレンの使用条件（エチレン濃度が貯蔵期間の最終まで最大 4 ppm であること）から、酸化エチレン濃度が許容できない遺伝毒性および発がん性の危険を起こすレベルに達することはあり得ないと考えられる。

文献上、エチレンの使用についてリスクアセスメントのための十分な情報がある。その情報に基づくと、エチレンは低毒性であり、低毒性麻酔剤として広く用いられていた。低レベルのエチレン暴露、エチレンの低吸収率およびエチレンの酸化エチレンへの低変換に基づいて、酸化エチレン濃度が認容できないレベル（＞1.0 ppm）に達するとは考えられない。エチレンは、貯蔵ジャガイモの萌芽抑制のための植物成長調節剤としての使用条件のもとでヒトに対して無害であると結論できる。製品ラベルの表示に基づいて提案された使用条件を厳守すれば、エチレンの危険性はないと考えられる。

3.2 一日摂取許容量の決定

HPBHC（カナダ健康省、健康保護支局）発刊の”健康・安全状況報告”（1994 年5月）には、エチレンの ADI （一日摂取許容量)は要求されていない。それは、エチレンが果物やジャガイモを含む野菜類の老化とともにに自然に生じるからである。エチレンはまたヒトや室内家畜において自然に生じる内生化学

物質であり、暴露していないラットやヒトの呼吸によっても放出されるため大気中からも検出される。潜在的なエチレン代謝は自然にも存在している。処理ジャガイモにおける代謝産物の分析データには、残留レベルが検出限界レベル以下または対照区とほぼ同じレベルであると示されている。

3.3 急性参照用量

エチレンが急性危険性でないことから、急性参照用量(ARfD)は算定されていない。文献では、急性食事危険評価の事項に関して有意な処理証拠はないとされている。低毒性であることそして麻酔剤として広く使用されていたことから、エチレン暴露によるヒトの潜在的危険性は無視してもよいと考えられている。

3.4 毒性エンドポイント選抜:業務従事者および第三者危険評価

暴露の一次的ルートは吸入である。エチレンは吸入ルートを通しても低急性毒性である。エチレンは単純な麻酔剤と考えられている。文献上から、Sprague-Dawley ラットを用いた亜慢性吸入実験では 10000 ppm(試験中最高量)でも毒性効果はみられなかった。Fischer 344 ラットを用いた毒性／発ガン性吸入実験では、処理区に有意な結果は見られず、また 3000 rpm の濃度(試験中最高濃度)でも発がん性の証拠はみられなかった。圧縮ガスとしてエチレンに接触すると皮膚と目にやけどを起こすことがあり、可燃性による危険性がある。このタイプの暴露の可能性は表示(注意事項)を厳守することよって軽減することができる。このような表示はこの活性成分の最も適切な規制アプローチと考えられ、エチレン使用上の暴露と危険性の質的評価が実施されている。

3.5 活性物質またはその不純物暴露によるヒトと動物の健康に対する影響

3.5.1 オペレーターの暴露評価

貯蔵ジャガイモへの適用

Eco Sprout Guard は、種々の濃度(2から 100%)の圧縮エチレンガスからなり、シリンダー容器に充填されている。窒素ガスを補充することでバランスをとっている。Eco Sprout Guard は、ジャガイモ貯蔵施設の空調システムで貯蔵期間中 4 ppm の濃度でエチレンガスを放出することによって効果が得られる。最もよい結果を得るためには、ジャガイモを収穫後1−7日で処理を開始し、加工前1−7日まで処理を継続することである。貯蔵業務従事者は、規定のガス濃度を示す濃縮エチレンガス容器を管理しなければならない。貯蔵施設内のガス濃度は注入速度とエチレン濃度(%)によって決定される。貯蔵建物内のエチレン濃度はモニターされ、継続的に遠方からでも貯蔵期間を通して目標レベルに近い値であることを確認しなければならない。一般的には、エチレンガス注入システムは、建物内で空調条件に応じてバルブを操作するためのプログラム制御法を用いている。システム自身は自動的に組み込まれているが、パラメーターの設定、容器の連結と取り外し、使用済み容器やシステムの欠陥箇所の取り替えの場合には人の介入が必要である。

オペレーターへの暴露

作業従事者へのエチレンの暴露は、エチレン処理中に貯蔵建物に入室時、循環ダクト工事中(例え

ば修理のため）あるいはベンチレーションの排出口の近くにいる時におこる可能性がある。暴露の基本的ルートは吸入である。

エチレンは、植物と動物によって作られる自然発生ガス状化学物質である。ほとんど付随毒性なしに麻酔剤（麻酔剤は酸素中 80-90%のエチレンを暴露することで使用される）として使用された長い歴史がある。一般に米国では安全性であることの確認（GRAS）がなされている。ACGIH(米国産業衛生専門家会議)では、エチレンの暴露限界は示されていない。ACGIH はエチレンを“単純な窒息剤”として分類している。単純な窒息剤使用の場合、緊急時または未知の濃度の施設に意図的に入室する場合または酸素欠乏の場所を除いて、呼吸保護は必要とされていない。文献上、亜急性吸入毒性実験では、Sprague-Dawley ラットで 10000 ppm（試験中最高量）まで、毒性効果はみられなかった。ラットを用いた2年間の長期吸入実験でも 3000 ppm (1 日6時間、週5日間)の暴露で影響がないことが示された。このことから、指定された条件で用いる場合、吸入によってエチレンに暴露された従事者の危険性の可能性は無視できると結論される。

高濃度のエチレンの暴露は、密閉施設でリークしたときに生じる可能性がある。予防説明書には、ガス容器の適切な取り扱いとリークを防ぐためのガス放出システムについて示されている。同じように登録者は使用者に対して、エチレンガスの放出と監視を代用する設備についての情報を提供している。未知の濃度のエチレンガス使用施設に入室する場合、呼吸保護は図面表示に従うことが大切である。これらの予備説明は適切であると考えている。

圧縮ガス容器の取り扱いや圧力のかかった設備では、その可燃性による危険性、液体ガスによる急性皮膚または目への暴露の可能性（皮膚や目に接触した場合にやけどを起こす）が示されている。この危険性は適切な保護設備の使用によって適切に軽減することができる。長めのスリーブ、長めのズボン、ゴーグルまたはフェイス・シールド、適切なグローブの着用を勧める。

3.5.2 第三者

Eco Sprout Guard の適切な使用形態に特性から第三者への暴露の可能性は無視できる。

3.5.3 作業者

作業者は、ベンチレーションが終了する前にエチレン処理中または処理後に貯蔵場所（例えば点検のため）に入ることができる （3.5.1 を参照）

4 残 留

本請願では、残留についてのデータは提出されていない。しかし、ジャガイモ萌芽抑制剤としてエチレンを登録するためにすでにデータが提出されている。その情報は 1994 年5月にエチレンのための“健康・安全状況報告”の中のカナダ健康省健康保護支局によって要約されている。この報告から抜粋した情報をこの章に記載する。

エチレンの代謝作用は、ジャガイモでは特別に調べられていないが、多くの植物で調べられているエチレン代謝および代謝経路と類似しているかほとんど同じである。老化組織としてのジャガイモ塊茎では、エチレンはもしあったとしても非常にゆっくり代謝されるため、基本的には低いエチレン代謝速度である。内生濃度は、未萌芽塊茎で 0.0007-0.15 ppm、萌芽塊茎で 0.1-3ppm の範囲である。エチレンが低浸透性であることを加味すると貯蔵塊茎中のエチレン代謝は低濃度であると予想される。

エチレンとその可能な代謝産物について、処理ジャガイモと対照の無処理のジャガイモとの間には検出レベルに有意な差はみられない。それ故に評価として動物代謝と家畜の飼料の研究は必要がないと考えられる。

4 ppm のエチレンを 150 日間処理したジャガイモについてエチレン残留のデータがある。クロロエタノール、ジクロロエタン、ブロモエタノール、酸化エチレンおよびエチレングリコール(そのグルコサイドを含む)の残留は全体で 0.1 ppm 以下であった。最も毒性の高い代謝産物、酸化エチレンの残留は 2 ppm 以下であった。さらに、揮発性の残留物(酸化エチレン)は塊茎の加工や調理の過程で 90%まで低下すると予想される。この残留の散逸は、加工中のジャガイモ組織の拡散と調理中の加熱による揮発によって生じる。

ジャガイモ塊茎組織内のエチレンの分配係数は非常に低い(0.207)、このことは、もし代謝しているとしてもジャガイモ塊茎における ^{14}C-エチレンの 区別がほとんどできないことを示している。一般に土壌中には約 10 ppm レベルの内生エチレンを含む、そのレベルは土壌の湿度が高くなるにつれて増加する。代謝的に活性のある発達中のジャガイモ塊茎では、エチレン残留を代謝して生物濃縮すると予想される。1993 年と1994 年の実験で処理したジャガイモ塊茎の成熟塊茎について調べられたエチレン代謝産物の残留は LLQ 以上には至らなかった。

ジャガイモ塊茎内ではエチレンの不浸透性が証明されている。ジャガイモ塊茎は拡散に対して高い抵抗性をもつ。それは塊茎の表皮がガス状物質の拡散のバリアーになることと塊茎全体の約2%を占める非常に小さな組織を通して拡散されるためである。この状態が塊茎内における外生エチレンの移行を効率的にブロックしている(濃度こう配に対しても)。それによって塊茎内のエチレンの内部濃度は内生レベルで維持されている。

エチレンを処理したジャガイモについて加工実験は行われていない。しかしながら、処理した塊茎をフレンチフライ、パウダーポテト、ポテトフラワーまたは生のジャガイモ料理に加工すると、最も注目される酸化エチレンの残留がもしバックグラウンド以上のレベルにあったとしても非常に減少する。酸化エチレンは室温ではガスであり、12C 以下では液体である。調理中にジャガイモから蒸発されると考えられる。

提出データによると、常法によって処理されたジャガイモでは、エチレンまたその主要な代謝物は無処

理レベル以上には残留しない。それ故に、食物としての危険評価の必要性がなく、MRL は提案されていない。

5 環境における運命と性質

5.1 環境に関係のある物理化学的性質

エチレンの物理化学的性質は表 5.1(省略)に要約する。LSS とその他の種々のソースから集めた情報によって行われたレビューに基づいている。活性成分は 98.5%以上である。

環境化学と運命実験の要約

エチレンの環境運命についてのデータは、このガスは自然に存在するため、要求されていない。

予想される環境濃度

貯蔵でのエチレンの使用は大気中におけるエチレンの EEC(予想される環境濃度)に影響をあたえる。しかし、使用場所から大気濃度へのエチレンの貢献は無視してもよいと考えられる。

自然および人為的に発生されるエチレンガスの 89%は、対流圏では OH-ラディカルによって分解され、8%はオゾンと反応して破壊される。約3％は成層圏に運ばれる。大気中に放出されたエチレンの寿命は約2−4日である。

6 非標的種に対する影響

（省略）

7 有効性

（省略）

8 毒性物質管理方針

（省略）

9 提案された規則決定（PRD）

（省略）

資料　8

英国（EU 連合）におけるエチレン登録の現状
食料環境保護法令 1985
農薬規則条例 1986（SI 1986 No.1510）：承認
2006 年５月 19 日発刊

農薬の承認

エチレン（99.9%）

Schedule: Commodity Substance: 99.9% v/v Ethylene

Food and Environment Protection Act 1985
Control of Pesticides Regulations 1986 (SI 1986 No. 1510): Approval

Date of issue: 19 May 2006

Date of expiry: 31 December 2013 (unless earlier decisions are made or further prescribed extensions are granted)

Notice is hereby given that in exercise of the powers conferred by Regulation 5 of the *Control of Pesticides Regulations 1986 (SI 1986/1510) (as amended)* and of all other powers enabling them in that behalf, the Secretary of State, and the Scottish Ministers (as regards Scotland) and the National Assembly for Wales and the Secretary of State (acting jointly as regards Wales) have given full approval for use of the following commodity substance: Commodity substance: being 99.9% v/v Ethylene.

This Approval is Subject to the Following Conditions

Field of use

Only as a plant growth regulator in food storage practice.

Situations

Post harvest crops.

Target atmospheric ethylene concentrations

- 150 ppm (172.5 mg/m^3) in fruit ripening;
- 100 ppm (115 mg/m^3) in onion storage;
- 50 ppm (57.5 mg/m^3) in potato storage.

Operator protection

1. Engineering control of operator exposure must be used where reasonably practicable in addition to the following personal protective equipment: Operators must wear suitable self-contained breathing apparatus in atmospheres with an ethylene concentration exceeding 1000 ppm (0.1% v/v; 1150 mg/m^3).

2. However, engineering controls may replace personal protective equipment if a Control of Substances Hazardous to Health (COSHH) assessment shows they provide an equal or higher standard of protection.

Other Specific Restrictions

1. Handling and release of ethylene must only be undertaken by operators suitably trained and competent to carry out the work.
2. Operators must vacate treated areas immediately after ethylene introduction.
3. Unprotected persons must be excluded from the treated areas until atmospheres have been thoroughly ventilated (for 15 minutes minimum before re-entry).
4. Ambient atmospheric ethylene concentration must not exceed 1000 ppm (0.1% v/v; 1150 mg/m^3). Suitable self-contained breathing apparatus must be worn in atmospheres containing ethylene in excess of 1000 ppm.
5. A minimum 3 day post treatment period is required before removal of treated crop from storage.
6. Ethylene treatment must only be undertaken in fully enclosed storage areas that are air tight with appropriate air circulation and venting facilities.

Advisory Notes

See also HSE Local Authority Circular 31/2 July 2000 (Revised November 2004).

Further Information

Approval of Commodity Substances

The Applicant Guide: Details of application procedures for approval of commodity substances.

Code of Practice for Using Plant Protection Products (replaces "Green Code")

Guidance Concerning the Approval of Ethylene and Ethanol Based Products as Pesticides - Regulatory Update

Guidance Concerning the Approval of Ethylene and Ethanol Based Products as Pesticides

The purpose of this update is to remind manufacturers and users of the approval requirements that apply to the use of ethylene as a pesticide. This includes the use of products containing ethanol to produce ethylene. For the purpose of this update the term 'marketing' means the sale, supply, storage and advertisement of pesticide products.

Background

On 2 August 2005 the Pesticides Safety Directorate published a new commodity chemical approval for the use of the commodity chemical 99.9% v/v ethylene in fruit ripening, onion storage and in potato storage. This type of approval relates only to the **use** of ethylene; it does not permit the marketing of pesticide products containing ethylene or ethanol labeled for use as a growth regulating pesticide. The placing on the market of any such products is an offence.

Any company wishing to market ethylene or an ethanol based product for generating ethylene as a pesticide, must apply to PSD in the usual way for a product approval to market the product under an approved label.

PSD has received a number of queries in the past about the approval of ethylene generators in their own right. Our regulations apply only to pesticides; they do not cover equipment employed in the manufacture, use or application of pesticides.

Both ethanol and ethylene are being supported for inclusion in Annex I of European Community (EC) Directive 91/414 as part of the fourth stage of the EC review programme. If it is agreed that these compounds are to be included in Annex I, the existing commodity chemical approval will be revoked. This is because only approvals for products marketed as pesticides are recognised by the EU. At the risk of pre-empting whether ethylene may be included, any company wishing to supply ethylene products to

the market for use as a pesticide after inclusion on Annex 1 (which could be in 2007, but may not be until 2008), should be thinking now about seeking a product approval.

Guidance on how to submit a package to support Annex I inclusion is included in the Applicant Guide on the PSD website. Information on registering a product is also available on our website.

You should note that this principle also applies to all other commodity approvals. If a pesticide product is approved ahead of the commodity chemical's inclusion in Annex I, both the commodity chemical approval and that for any product approval will exist side by side until the commodity chemical use is revoked. We will issue further guidance on this in due course.

Contact Information

If you would like any further information or have any questions on the above, please contact either Matthew Wells on 01904 455749, email: matthew.wells@hse.gsi.gov.uk, or Mark Wilson on 01904 455705, email: mark.wilson@hse.gsi.gov.uk.

Regulatory Update

Regulatory Update: 22/2005

Issued: 20 October 2005

(参考資料)英国(EU 連合)におけるエチレン登録の現状

農薬の承認、商品物質:エチレン

スケジュール:汎用物質:エチレン(99.9%)

食料環境保護法令 1985

農薬規則条例 1986(SI 1986 No.1510): 承認

2006 年5月 19 日発刊

2013 年 12 月 31 日効力消失

本通知文は、CPR 農薬規制法 1986 (SI 1986/1510)(改正案として)の規則5条によって協議されたものであり、次の汎用物質使用のための完全な承認を与えることである:汎用物質とは 99.9%エチレンであること。

本承認は次のような条件に従うことである

使用分野:

食品貯蔵のための植物成長調節剤としてのみ使用。

状況:

収穫後の作物

目標の大気エチレンの濃度:

果物の熟成、150 ppm (172.5 mg/m^3)

タマネギの貯蔵、100 ppm (115 mg/m^3)

ジャガイモの貯蔵、50 ppm (57.5 mg/m^3)

オペレーターの保護:

1, オペレター汚染への技術的制御は、次のような身体防御装置に加えて合理的に実施できる場所で使用しなければならない:オペレーターはエチレン濃度 1000 ppm を超えない適切な自給式呼吸器を装備しなければならない。

2, しかしながら、もし COSHH 評価委員が同等または高水準の保護を用意していると判断される場合は、技術的制御は身体保護装置に置き換えることができる。

その他の特別規制:

1、 エチレンの取り扱いと放出は、その仕事を行える適度に訓練された有能なオペレーターによって実施されること。

2、 オペレーターはエチレン注入後、直ちに処理場所から退去すること。

3、 保護装備をしていない人は、大気が完全にベンチレートされるまで処理場所から離れなければならない（再注入前最短15分間）

4、 大気中のエチレン濃度は1000 ppmを超えないこと。1000 ppmを超えるところでは、適切な自給式呼吸器を装備すること。

5、 貯蔵庫から処理作物を除去する前には、最短3日間の後処理期間を必要とする。

6、 エチレン処理は、適切な空調設備を備えた気密性のある完全に密閉された貯蔵庫で実施すること。

農薬としてのエチレン製品の承認に関する指針

本更新(改正)の目的は、エチレンを農薬として使用申請するための生産者と使用者に対する承認要件を通知することである。これには、エチレンを生じるエタノールを含む製品の使用も含まれる。この最新情報の意図する“マーケティング”いう定義は、農薬の販売、供給、貯蔵および広告を意味する。

背　景:2005年8月2日にPSD（農薬安全総局）は、）を果物の成熟、タマネギの貯蔵、ジャガイモの貯蔵における汎用化学物質エチレン（99.9%）の使用に対する新たな汎用化学物質に認可を公開した。この認可は、エチレンの使用のみに限定している:つまり成長抑制農薬として使用表示のあるエチレンやエタノールを含む製品のマーケティングは許可していない。そのような製品の上市は違法である。エチレンを農薬として市場に出したい会社は、正規な手続きを経て、PSDに申請しなければならない。

資料　９

OECD: Screening Information Data Set(SIDS)
（経済開発協力機構：審査情報データセット：エチレン
1998 年 10 月

ETHYLENE

CAS N°: 74-85-1

（後半に和訳を添付）

FOREWORD INTRODUCTION

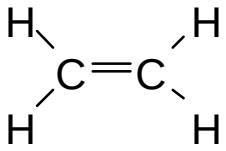
ETHYLENE

CAS N°: 74-85-1

SIDS DOSSIER ON ETHYLENE

Summary of Responses to the OECD Request for Available Data on HPV Chemicals

SIDS PROFILE

1.01 A	CAS NO.	**74-85-1**
1.01 C	CHEMICAL NAME	Ethylene
1.01 G	STRUCTURAL FORMULA	
	OTHER CHEMICAL IDENTITY INFORMATION	
1.5	QUANTITY	Millions metric tonnes per year: (capacity for 1996) Norway: 0.4 World: 83.0
1.7	USE PATTERN	Chemical industry; as raw material for synthesis of chemicals, petrochemicals and resins. Minor quantities used for fruit ripening and as anaesthetic gas.
1.9	SOURCES OF EXPOSURE	Fuel, coal and gas combustion. Leakage from chemical industry. Rural areas: < 1 - 5 $\mu g/m^3$ (0.9 - 4.3 ppb) Heavy traffic areas: up to 1.0 mg/m^3 (0.9 ppm) Petrochemical plants: up to 5 mg/m^3 (4.3 ppm)
ISSUES FOR DISCUSSION (IDENTITY, IF ANY)	No further testing required	

1. GENERAL INFORMATION

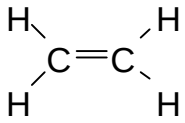
A. **CAS number:** 74-85-1

B. **Name** (IUPAC): Ethylene

C. **Name** (OECD): Ethylene

F. **Molecular formula:** CH_2CH_2

G. **Structural formula:**



H. **Substance group:** Industrial chemical; as raw material for synthesis of chemicals, petrochemicals and resins.

J. **Molecular Weight:** 28.05

1.02 OECD INFORMATION

A. **Sponsor Country:** Norway

B. **Lead Organisation:**
Norwegian Pollution Control Authority (SFT),
P.O. Box 8100 Dep.,
N-0032 Oslo
NORWAY

Contact person:
Marit Kopangen

Tel.: +47 22 573400
Fax.: +47 22 676706

C. **Name of responder:**
Noretyl ANS,
Petrochemical division,
Norsk Hydro ANS,
N-0240 Oslo
NORWAY

1.1 GENERAL SUBSTANCE INFORMATION

A. **Type of Substance:** Organic, hydrocarbon

B. **Physical state** (at 20 ^{o}C and 1.013 hPa): Gaseous

C. **Purity:**

1) High purity : > 99.9 %
2) Commercial purity : about 99.9 %

1.2 SYNONYMS

Ethene, acetene, bicarburetted hydrogen, olefiant gas, elayl.

1.3 IMPURITIES

Western Europe product, (ppm range)**:**
Methane + ethane (50-200), propylene and heavier (7-200), CO_2 (2.2-50), H_2(0.1-10), O_2 (0.6-10), acetylene (1.4-10), total sulphur (1-10), water (0.6-20) and CO (0.15-10) [3].

1.4 ADDITIVES

None known.

1.5 QUANTITY

More than 1,000,000 tonnes per annum.
Capacity for 1996 [2]:
Norway: 405,000 tonnes
World: 83,000,000 tonnes

1.6 LABELLING AND CLASSIFICATION

EEC: Fx, R12 (Extremely flammable).
S 2 (Keep out of reach of children.
S 9 (Keep container in well-ventilated place)
S 16 (Keep away from sources of ignition - No smoking)
S 33 (Take precautionary measures against static discharges)

Norway: F, R13 (Extremely flammable liquid gas)
S 9-16-33

According to IARC Monograph Volume 60, (1994):
Ethylene: The agent is not classifiable as to its carcinogenicity to humans [3].

1.7 USE PATTERN

Ethylene is the petrochemical product produced in largest quantities world-wide. More than 95% of the annual commercial production of ethylene is currently based on steam cracking of petroleum hydrocarbons [4].

About 80 % of the ethylene consumed in US, Western Europe and Japan is used for production of ethylene oxide, ethylene dichloride and low density, linear low density and high density polyethylene. Significant amounts are also used to make ethylbenzene, alcohols, olefins, acetaldehyde and vinylacetate. Most of these products are further prosessed into products such as film, blow and injection moulding, extrusion coating, cable insulation and PVC. Minor quantities have been used as anaesthetic gas, for fruit ripening and for welding and cutting metals.

A. General

	Type of use:	Category:
a)	Main industrial use	Use in closed systems Chemical Industry: used in synthesis Raw material
b)	Main industrial use	Non dispersive use Agricultural Industry As fruit ripener

B. Uses in Consumer Products
Not known

1.8 OCCUPATIONAL EXPOSURE LIMIT VALUE

No exposure limits have been recommended in most countries, but Switzerland established a time-weighted average occupational exposure limit of 11 500 mg/m^3 [3].

1.9 SOURCES OF EXPOSURE

Ethylene is ubiquitous in the environment, arising from both natural and man made sources. Major sources are as a natural product from vegetation of all types [5].
The main anthropogenic sources are from combustion of gas, fuel, coal and biomass. Maximal exposure of ethylene to humans is considered to be through fossil combustion by vehicles. The total ethylene emission from the global surface has been estimated to be 18-45 $\cdot 10^6$ t/y, of which approximately 74% is released from natural sources and 26 % from anthropogenic sources. Emission from oil combustion is estimated to 1.54 $\cdot 10^6$ t/y [5]. Ethylene produced and consumed in chemical industry is kept in closed systems and the production facility is normally next door to the factory using ethylene as a raw material. Exposure to ethylene from industrial sources are thus mainly due to uncontrolled leakage or blow outs. Such events occur at a rate of once every 2.0 $\cdot 10^6$ t/y of produced ethylene and may result in an immediate release of about 1 ton.

1.10 ADDITIONAL REMARKS

A. Option for disposal
Incineration.

B. Other remarks
No data.

2. PHYSICAL-CHEMICAL DATA

2.1 MELTING POINT

-169.15 °C [4]

2.2 BOILING POINT

-103.71 °C [4]

2.3 DENSITY

d = 0.57 g/cm^3 at boiling point [4].
Gas density at STP 1.2603 g/l [4].
Density relative to air 0.9686 [4].

2.4 VAPOUR PRESSURE

4.27 MPa at 0 °C [4].

2.5 PARTITION COEFFICIENT $\log_{10}P_{ow}$

$Log_{10} P_{ow}$ = 1.13 (calculated) [6].

2.6 WATER SOLUBILITY

A. Solubility

According to Merck Index, "One volume of ethylene gas dissolves in 4 vol of water at 0°C" [7].
One volume of ethylene gas dissolves in 9 volumes of water at 25 °C [8].
Solubility: 131 mg/l at 20°C [9].
At 15 °C the solubility in water is 200 mg/l [10].

B. pH Value, pKa Value

No data available. There is no chemical evidence to suggest a reaction between dissolved ethylene and water and pH remains unchanged.

2.7 FLASH POINT

- 136.11 °C [11].

2.8 AUTO FLAMMABILITY

Autoignition temp: 543°C [7].
Ignition temp: 425-527°C [4].

2.9 FLAMMABILITY

Extremely flammable - liquefied gas.

2.10 EXPLOSIVE PROPERTIES

Explosive limits in air (0.1 MPa and 20°C) [4] :
Lower explosive limit (LEL): 2.75 vol %
Upper explosive limit (UEL): 28.6 vol %

2.11 OXIDIZING PROPERTIES

No information

2.12 OXIDATION:REDUCTION POTENTIAL

No information.

2.13 ADDITIONAL DATA

A. Partition co-efficient between soil/sediment and water (Kd).

No information

B. Other data

Conversion factor for ethylene in air:
1 ppm in air = 1.15 mg/m^3 = 912 nl/l [1,4]

Odour threshold:
Odour low: 299 mg/m^3
Odour high: 4600 mg/m^3 [12]

3. ENVIRONMENTAL FATE AND PATHWAYS

3.1 STABILITY

3.1.1 STABILITY IN AIR

The fate of atmospheric ethylene emitted from natural and anthropogenic sources has been estimated by Sawada and Totsuka, 1986 [5]. They concluded that 89 % was destroyed in the troposphere by reaction with OH radical, and 8 % in the reaction with O_3. The remaining 3 % was transported into the stratosphere. The atmospheric lifetime of ethylene was estimated to be between 2 and 4 days.

Indirect calculation of photodegradation with O_3 as a sensibilizer gave a lifetime of 9.4 days [13]. Using OH as the sensibilizer a lifetime of 2.7 days was calculated [14].

The following lifetimes are according to Howard, P.H. et al (1991) [15]: Handbook of environmental degradation rates:

		Lifetimes:
Air:	High:	3.36 days
	Low:	0.37 days

This is based upon combined, measured photoxidation rate constants for $^{\cdot}OH$ and O_3.
If the calculation procedures for organic compounds in atmosphere of Atkinson, R. (1996) [75] are used the following depletion rates are found:

		Lifetimes	
Air	Due to $^{\cdot}OH$ reaction	1.7	days
	Due to O_3 reaction	10	days
	Due to stratospheric removal	1900	days

Stratospheric removal can be calculated according to IPPC (1995) [76], assuming a similar removal of ethylene as CO.

3.1.2 STABILITY IN WATER

No data available

3.1.3 STABILITY IN SOIL

No data available

3.2 MONITORING DATA (ENVIRONMENT)

Rudolph and Johnen, [16] did more than 200 in situ measurements of ethylene and other selected Light Atmospheric Hydrocarbons during, a cruise from Puerto Madryn (Argentina) to Bremerhaven (Germany) in 1987. The measuring locations were remote with low biological activity in the surrounding ocean areas. The ethylene level, expressed as mixing ratio was in the range 10-30 ppt (12-35 ng/m^3) in the southern hemisphere and in the northern hemisphere a factor of 2 higher. The observed ethylene levels were primarily a result of oceanic emissions and the differences were indicated to be caused by changes in oceanic phytoplankton concentration.

The oceanic distribution of ethylene and other low molecular weight (LMW) hydrocarbons has been studied by Swinnerton and Lamontagne, 1974 [17]. They analyzed 452 water samples from the open ocean and near shore for LMW hydrocarbons and found a baseline (average) ethylene of: 4.8 nanoliters/litre (6.0 µg/l) . Upper values were: Mississippi R. Delta ; 35.0 nl/l (44 µg/l) and Miami dockside; 30.0 nl/l (38 µg/l).

Fuel, coal and gas combustion. Leakage from chemical industry. Rural areas: < 1 - 5 µg/m^3, heavy traffic areas: up to 1.0 mg/m^3 [1, 3].

During burning of wood (white pine) an ethylene concentration of about 50 ml/m^3 (63 mg/m^3 was measured in the smoke [18].

3.3 TRANSPORT AND DISTRIBUTION BETWEEN ENVIRONMENTAL COMPARTMENTS INCLUDING ESTIMATED ENVIRONMENTAL CONCENTRATIONS AND DISTRIBUTION PATHWAYS

In their study of the dynamics of atmospheric ethylene, Sawada and Totsuka, [5] estimated the following emissons of ethylene (in 10^6 t/y):

Natural:		
Terrestrial	23.3	(65.8 %)
Aquatic	2.9	(8.2 %)
Sum	26.2	(74.0 %)
Anthropogenic:		
Fuel oil combustion	1.5	(4.28 %)
Coal cumbustion	0.42	(1.20 %)
Leakage from Industri	0.03	(0.09 %)
Søpel forbrenning	0.10	(0.29 %)
Biomass burning	7.10	(20.1 %)
Sum	9.19	(26.0 %)

Total Natural + Anthropogenic = 35.4 $\cdot 10^6$ t/y

Atmospheric depletion of ethylene:
Ethylene reacts with OH radical to form an adduct which in the presence of O_2 and NO_x forms formaldehyde. The products of reaction of ethylene with O_3 are mostly CO, CO_2, H_2O and CH_2O. Some ethylene is also transported into the stratosphere [76]. Using the most recent

estimates [75] of the depletion rates (lifetime) of ethylene in the atmosphere due to these prosesses give:

:

	lifetime (days)	
Reaction with ·OH radical	1.7	
Reaction with O_3	10	
into the stratosphere	1900	
total lifetime in atmosphere	1.45	
Ethylene sinks (removal capacity, 10^6 tons/y):		
Reaction with ·OH radical	44.4	(85.4%)
Reaction with O_3	7.5	(14.5 %)
Into stratosphere	0.036	(0.07 %)
Sum	52.0	

The ethylene transported into the stratosphere will eventually react with O_3 with the production of a krøger molecule, which again may react with NO regenerating O_3. ethylene is therefore not suspected of being a potential ozone depletor.

3.3.1 TRANSPORT

Physical properties of ethylene indicate that it will rapidly move into the atmosphere from any type of release.

3.3.2 THEORETICAL DISTRIBUTION (FUGACITY CALCULATION)

A fugacity level I calculation, using a six compartment model (air, water, soil solids, sedimented solids, suspended sediments and fish) was conducted using the global reference model of OECD [19]. Default values for the environmental parameters were not changed. Entered generic parameters were: melting point - 169.15 ^oC, vapour pressure 4.27 MPa, water solubility 200 g/m^3, $\log_{10}P_{OW}$ 1.13, half-life in air 56 hours, half-life in water, soil and sediment 672 hours. This gave the following distribution:

in air	99.99915 %,
in water	$8.27 \cdot 10^{-4}$ %,
in soil solids	$9.88 \cdot 10^{-6}$ %
in sedimented solids	$2.20 \cdot 10^{-7}$ %.
in suspended sediments	$6.87 \cdot 10^{-9}$ %
in fish	$5.58 \cdot 10^{-10}$ %

This means that for all practical purposes, emitted ethylene is distributed to air only.

3.4 IDENTIFICATION OF MAIN MODE OF DEGRADABILITY IN ACTUAL USE

See 3.3

3.5 BIODEGRADATION

Also a number of research orientated studies were designed to examine the oxidation/hydroxylation and epoxidation of various hydrocarbons by microorganisms isolated from soil, fresh water systems or other natural systems and pure cultures. Generally, results of these studies show that ethylene is subject to biodegradation by various microorganisms and that ethylene oxide and ethylene glycol are most likely initial degradation products [21].

Aqueous biodegradation rates have been estimated both for aerobic and anaerobic conditions [15]:

Aerobic half-life:	High:	672 hours
	Low:	24 hours
Anaerobic half life:	High:	2688 hours
	Low:	96 hours

3.6 BOD_5, COD OR RATIO BOD_5/COD

No data available

3.7 BIOACCUMULATION

Ethylene is not expected to bioaccumulate because of $Log_{10} P_{ow} = 1.13$.
BCF (Bioconcentration factor) is calculated (QSAR) to be 4 on the basis of the toxic action of nonpolar molecules in the freshwater fish Fathead minnow (pimephales promelas), exposure duration 2.00 - 304 days [22].

3.8 ADDITIONAL REMARKS

No data.

4. ECOTOXICOLOGICAL DATA

4.1 ACUTE TOXICITY TO FISH

Little is known about the acute toxicity of ethylene to fish, but the "Water Quality Criteria, California State Water Resources Control Board, 1963" [23] refers to two reports of toxicity of ethylene to Orange-spotted sunfish from 1917 [24] and 1921 [25]. The findings were the following:

Lethal conc after 1 hour :	22 - 25 mg/l [24]
Lethal conc after $\geq$ 1 hour :	22 - 65 mg/l [25]

Calculated (QSAR) values reported in the database Ecotoxicity Profile database [26]:

Fathead minnow (*Pimephales promelas*)	4 days LC_{50} 116 mg/l
Bluegill, (*Lepomis macrochirus*)	4 days LC_{50} 85 mg/l
Channel catfish, (*Ictalurus punctatus*)	4 days LC_{50} 50 mg/l
Rainbow trout, Donaldson trout, (*Onchorhynchus mykiss*)	4 days LC_{50} 55 mg/l

Calculated (QSAR) values reported by Leeuwen et. al. [27]:
Fathead minnow (Pimephales promelas) 4 days LC_{50} 120 mg/l

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

A. Daphnia

Calculated (QSAR) value reported in the database Ecotoxicity Profile [26]:
Water flea, (Daphnia magna) 48 hours LC_{50} 53 mg/l

Calculated (QSAR) value according to Leeuwen et. al. [27]:

Daphnid	48 hours	LC_{50}	153 mg/l

B. Other aquatic organisms

No data available.

4.3 TOXICITY TO ALGAE

A growth inhibition test with *Selenastrum capricornutum* was performed according to OECD 201 and conducted according to GLP guidelines in 1996 [74]. The 5 nominal test concentrations in the growth medium ranged from 8.2 to 131 mg/l. During the 72 hr exposure period there was a loss of ethylene, however the mean measured ethylene concentrations (mean of zero time and 72 h measurement) were used for calculation of growth inhibition. Actual test concentrations (mean) were therfore: 3.3, 7.8, 13.9, 32 and 58mg/l. Loss of ethylene during the 72 hr incubation period ranged from 64 to 91 %. EC_{50} for the growth inhibition based on reduction in biomass compared to control, was calculated to be 40 mg/l (95 % conf. lim.36-46 mg/l). Based on the specific growth rate (μ), the 0 - 72 hr EC_{50} was calculated to be 72 mg/l (95 % conf. lim. could not be calculated due to that the EC_{50} value was outside the range of the test). The highest NOEC was 13.9 mg/l. The results agree fairly well with QSAR calculation for *Selenastrum capricornutum* which gave an EC_{50} after 48 hour value of 122.5 mg/l [27].

4.4 TOXICITY TO BACTERIA

E.coli bacteria were treated with ethylene by passing the gas through a bacterial suspension at constant rate for 10 minutes. After 24 hours exposure, the suspensions were plated on agar medium and incubated for 24 hours at 37 ℃. Survival of colonies from gas treated cells was 79 ± 1.3 % of controls. The survival of the *E. coli* Sd-4 strain after the same treatment was 84.2 ±1.6 % compared to controls. It was concluded that treatment seemed to have little if any effect on the survival of both bacteria strains [28].

4.5 CHRONIC TOXICITY TO AQUATIC ORGANISMS

4.5.1 CHRONIC TOXICITY TO FISH

Calculated (QSAR) value reported in the database Ecotoxicity Profile [26]:

Fathead minnow, (Pimephales promelas)	32 days	MATC 15.3 mg/l

Calculated (QSAR) value according to Leeuwen et. al. [27]:

Fathead minnow, (Pimephales promelas) 28 days		NOEC 13 mg/l

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

Calculated (QSAR) value according to Leeuwen et. al. [27]:

Daphnia	16 days	NOEC 37.4 mg/l

4.6 TOXICITY TO TERRESTRIAL ORGANISMS

4.6.1 TOXICITY TO SOIL DWELLING ORGANISMS

No data available

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

A large and diverse literature exists on the effects of ethylene on vascular plants, including several hundred observations of ethylene exposure and effects. This is mainly due to the fact that ethylene acts as a plant hormone, regulating a whole range of different reactions. Most of these reactions can be categorised as growth regulation and include such effects as defloration, ripening, inhibition of elongation, leaf loss and senescence [9,11, 29, 30, 31, 32]. While most of these effects are non reversible, they do not all constitute effects that reduce a plants fitness nor growth and reproduction. One may categorise the effects into 3 groups based on assumed long term effects, where long term effects are associated with reduced fitness, growth or reproduction. In the table below exotic and tropical plants have been excluded in order to present data that give a more realistic view of risks associated with exposure in industrial areas.

Summary table of effects of ethylene exposure to vascular plants. Exotic and tropical plants are not included. Epinasty=leaf curling, Abcission=loss

Effects	exposure time	concentration $\mu g \cdot m^{-3}$	Ref
1) None or small long term effects:			
Epinasty, Lemon		25-50	[77]
Epinasty, tomato	3-4 h	46	[9]
Epinasty, *Chenopodium*		60	[9]
Epinasty, Potato	16 h	60	[9]
2) Effects that may cause long term effects			
Inhib growth, sweet pea, (NOEC)	2 d	12	[77]
Abscission flower, Carnation	2d	58	[77]
Inhibition of photosynth. Pea (NOEL)	2 h	115	[77]
Abscission flower, Snapdragon	1h	575	[33]
3) Long term effects:			
Decreased amount flowers, Oats	100d	8	[77]
Growth inhibition, Potato	28 d	27	[77]
Yield reduction, Tomato	28 d	50	[77]
Growth retardation, Pea		116	[9]
Yield reduction, Garden cress (30 %)	14 d	115	[77]
Yield reduction, Cotton	30 d	700	[9]

Among the more sensitive agricultural or horticultural crops are peas, potatoes, tomatoes and oats where retardation effects were observed at concentrations in the range 8-50 $\mu g/m^3$ (7-40 ppb) . The most susceptible non-woody plant reported, African marigold reacts with leaf epinasty (downward curling of leaves at 1.16 $\mu g/m^3$ (1.0 ppb) ethylene [9], the Cattleya orchid, reacts with sepal tissue collapse (loss of flower) at 2.3 $\mu g/m^3$ (2.0 ppb) after ethylene exposure for 24 hours [33].

4.6.3 TOXICITY TO OTHER NON MAMMALIAN TERRESTRIAL SPECIES (INCLUDING AVIAN)

No data

4.7 BIOLOGICAL EFFECTS MONITORING (INCLUDING BIOMAGNIFICATION)

No data

4.8 BIOTRANSFORMATION AND KINETICS IN ENVIRONMENTAL SPECIES

No data

4.9 ADDITIONAL REMARKS

No data

5. TOXICITY

5.1. ACUTE TOXICITY

5.1.1 ACUTE ORAL TOXICITY:

Not relevant. Ethylene is a gas with a low boiling point (-103.71 °C).

5.1.2 ACUTE INHALATION TOXICITY

The acute toxicity of ethylene is low, but very high concentrations may cause asphyxia due to oxygen displacement. The lethal ethylene concentration in air to mice is thus estimated to be 950,000 ppm. [34].

When male rats were exposed to 10, 25 or $57 \cdot 10^3$ ppm for 4 hours, all groups showed increased serum pyruvate and liver weight [35]. Non of the studies were GLP.

5.1.3 ACUTE DERMAL TOXICITY

Not relevant. Very little ethylene is likely to be absorbed through the skin because of ethylene's low solubility in fat and low boiling point.

5.1.4 ACUTE TOXICITY, OTHER ROUTES OF ADMINISTRATION

No information

5.2 CORROSIVENESS/IRRITATION

5.2.1 SKIN IRRITATION/CORROSION

There is no evidence to suggest that the liquid ethylene gas is irritant, but it might cause frost injuries.

5.2.2 EYE IRRITATION

There is no evidence to suggest that the liquid ethylene gas is irritant, but it might cause frost injuries.

5.3 SKIN SENSITISATION

No data.

5.4 REPEATED DOSE TOXICITY

The toxicity of ethylene has been tested in a 90 days inhalation study on 4 exposed and one control groups of 30 rats (15 males, 15 females) [36]. The animals were exposed 6 hours/day 5

days/week for 13 weeks. The exposure groups were T-I: 300 ppm, T-II: 1,000 ppm, T-III: 3,000 ppm and T-IV: 10,000 ppm. The study was not conducted according GLP, but the study held high scientific standard and a quality assurance statement was issued. There were no differences between controls and treated rats with respect to total weights, weight change, food consumption, haematology, clinical chemistry, gross pathology or histopathology. Male rats in the control, T-I and T-IV groups showed red deposits or red discharge around the nose, whereas the male T-II had red deposits around the eyes. Amongst the female rats, a red deposit was observed around left eye of one T-I rat and alopecia around both ears of one T-II rat. Compared with the controls, the liver weights in several groups of exposed rats were significantly lower. There was, however, no dose response relationship for this weight reduction and the cause was unknown. Ethylene was not toxic to rats when administered under a stratified regimen of exposure up to 10,000 ppm.

In an explorative non-GLP study, where a group of six male Sprague-Dawley albino rats (50-60 g) were exposed to a continuous flow of 60% ethylene in oxygen as inhalation for 6 days, effects could be seen on several haematology parameters [37]. There were significant reductions in thrombocyte count (-19.3%) and leukocyte count (-48.2%). A reduction was also seen in the bone marrow cellularity (-30%).

During chronic tests on rats (newborn) exposed to a concentration of 2.62 ppm (continuous as inhalation) for 90 days, a delay in coat appearance, dentition, eye opening and circulation hypotension, cholinesterase activity inhibition, subordination disruption were reported [38]. There were no information on the quality of the study.

In rats treated by inhalation with a concentration of 100 ppm for 70 days, a change in the reflex nerve impulses, a decrease of cholinesterase activity and a reduction of the blood pressure were observed [39]. There were no information on the quality of the study.

5.5 GENETIC TOXICITY IN VITRO

A. Bacterial test

Ethylene at atmospheric concentrations up to 20 % gave no indication of mutagenic potential in Salmonella typhimurium in the presence or absence of a metabolic activation system (Ames test) [40]. The study was not conducted according to GLP, and only one (TA 100) of the four bacterial test strains recommended in the guidelines was tested. Previous testing with the full range of Salmonella strains in the presence and absence of a metabolic activation system have also given negative results [41, 42]. Ethylene showed no gentoxic activity in Escherichia coli. [28].

B. Non-bacterial in vitro test

The effect of ethylene on chromosomes was tested in an in vitro cytogenetics assay using duplicate cultures of CHO cells [71]. The methodology in this study complies with GLP and the OECD Test Guideline 473, "Genetic Toxicology: In vitro Mammalian Cytogenetic Test". Treatments covering a broad range of doses, separated by narrow intervals, were performed both in the absence and presence of metabolic activation (S9) from Aroclor 1254 induced rats. The highest dose level used, approximately 280.5 mg/ml, was equivalent to a concentration of 10 mM, corresponding to about 25 % of ethylene.

Due to the explosive properties of the test article when mixed with air, it was not possible to achieve the maximum concentration required by the Regulatory Guidelines using air as carrier gas. Nitrogen was therefore used as carrier gas, which allowed higher doses to be achieved. There are, however, technical problems associated with continuous treatment in a nitrogen atmosphere, and short (3 hour) pulse treatments were the only practical option.

A preliminary range-finding study was performed to investigate the toxic effects of ethylene on CHO cells. In this trial, treatment in the absence and presence of S9 lasted for 3 hours only followed by a 17 hours recovery period prior to harvest (3+17). The dose levels for the main study were selected by evaluating the effect of ethylene on mitotic index.

The treatment regimes used in the range-finder were repeated in the main study. Chromosomal aberrations were analyzed at three consecutive dose levels. No mitotic inhibition (reduction in mitotic index) was observed at the highest concentration chosen for analysis (280.5 μg/ml) in either the absence or presence of S9.

Appropriate negative (carrier gas) controls were included in the test system in both experiments under each treatment condition. Untreated controls were also included in the main study. The proportion of cells with structural aberrations in the negative and untreated cultures fell within historical solvent control ranges. 4-Nitroquinoline 1-oxide and cyclophosphamide were employed as positive controls in the absence and presence of liver S9 respectively. Cells receiving these were sampled in the main study, 20 hours after the start of treatment; both compounds induced statistically significant increases in the proportion of cells with structural aberrations.

Treatment of cultures with ethylene in the absence and presence of S9 resulted in frequencies of cells with structural aberrations that were similar to, and not significantly different from, those seen in concurrent negative controls. Frequencies seen in treated cultures fell within the normal range.

It is concluded that ethylene did not induce chromosome aberrations in cultured Chinese hamster ovary cells exposed to a concentration of 10 mM (25 %) in the absence and presence of S9.

5.6 GENETIC TOXICITY *IN VIVO*

The effects on micronucleus formation in bone marrow cells of rats and mice have been studied following ethylene inhalation [43]. Each group consisted of 10 animals of each of the two species and they were dosed with concentrations of 0; 40; 1,000 and 3,000 ppm for 6 hours/ day, 5 days a week for 4 weeks. An ethylene oxide control group with both species was exposed using the same conditions at a concentration of 200 ppm. Bone marrow was collected approximately 24 hours after the final exposure. Ethylene did not produce, statistically significant, exposure related increases in the frequencies of micronucleated polychromatic erythrocytes in the bone marrow of either rats or mice, while ethylene oxide exposure resulted in signifcant increases in the frequencies in both species. It is not stated if the study was conducted according to GLP.

Absorption, distribution, elimination of ethylene and formation of haemoglobin and DNA adducts were studied in rats after inhalation of 300 ppm ethylene for 12 hours/day for 3 consecutive days [44]. DNA adduct formation was measured in liver and lymphocytes and haemoglobin adducts determined in erythrocytes. The adduct formation with ethylene was compared to other alkenes and adduct formation decreased with increasing number of carbon atoms in the molecule. This was an explorative study not conducted according to GLP.

Alkylation of 7-guanine was measured in DNA from liver spleen and testis of mice 14 hours after exposure by inhalation of ^{14}C-ethylene at an initial concentration of 11 ppm for 8 hours [45]. The degree of alkylation was much higher in the liver than in the other tissues. This study was an explorative non-GLP study.

5.7 CARCINOGENICITY

The potential carcinogenicity of ethylene has been tested in a two years study with rats (Fischer - 344 inbred) [46]. The study was conducted prior to OECD Guideline 451 for carcinogenicity testing (1981), but still the study comply with this guideline except for some minor points. In the study, 960 rats were randomly divided into 4 groups of 120 animals of each sex and exposed 6 hr/day, 5 days/week to 0(control); 300; 1,000 and 3,000 ppm for up to 24 months.

During the course of the study there were observations of hair loss, deposits on and around the nose and eyes and gross eye abnormalities, but there were no obvious differences among the different treatment groups.

There was an overall increase in the number of animals exhibiting gross tissue masses for the test groups as compared with the control group, although this trend was not statistically significant. The spontaneous mortality (15.7 %) was roughly equal in all treated groups. The final body weights and total weight changes for treated males were higher than those in the control groups, but no dose-related pattern was seen.

There were no statistically significant differences among any of the treatment groups on any of the haematology, blood chemistry or other parameters investigated.

No gross or histopathologic tissue changes attributable to the effects of the test material were observed in any of the treated rats. The summary reports only few findings which could indicate any carcinogenic effect of the treatment, but lacks a conclusion at this point.

In a publication from the carcinogenicity study [41], it was concluded that the results provided "no evidence that ethylene at these concentrations causes chronic toxicity or is oncogenic in Fischer - 344 rats". However, this publication and the summary have later been criticised [47] since they do not discuss the mononuclear cell leukaemia described in the full report. It was claimed that the number of animals affected (out of 90) rose from 12 and 8 in the male and female control groups to 21 and 11, respectively in the groups receiving 3,000 ppm. On the other hand, it has been stated that mononuclear cell leukemia may occur in F344 rats at a background incidence > 75 %, and that a further increase in exposed animals is difficult to interpret with respect to human cancer development.

When the carcinogenic risk of ethylene was evaluated by the International Agency for Research on Cancer (IARC) in 1979 [1], no data were available to the working group on the carcinogenicity or mutagenicity of the substance in animals and humans. In supplement 7 published in 1987 [48] it is still summarised that no adequate data were available and ethylene is stated to be not classifiable as to its carcinogenicity to humans. The latest evaluation of ethylene by the IARC working group (1994) concludes that there is inadequate evidence in humans and in experimental animals for the carcinogenicity of ethylene [3]. Overall, ethylene was evaluated as not being classifiable as to its carcinogenicity to humans.
In the Ecotoxicity Profile database it is stated to be no information in the QSAR system which would suggest that this chemical is a potential carcinogen or mutagen [26].

In another recent evaluation of ethylene as a cancer risk factor it was concluded that it was a risk factor of concern [49]. This conclusion was based on the observed metabolism of ethylene to ethylene oxide, a compound which has been shown to be both mutagenic and carcinogenic. The linearity hypothesis for dose response relationship can not be applied in this case, since there is a saturation of the metabolism of ethylene. The findings from administration of high doses to animals can thus not be extrapolated to the human exposure level.

The carcinogenic potential of ethylene has also been reviewed in the BIBRA Bulletin [50]. This review concludes also on the basis of metabolic production of ethylene oxide that it is timely with

a detailed reconsideration of the possible carcinogenic risks of inhaling ethylene. The evaluation also calls for re-evaluation of the need for a specific industrial limit of ethylene.

5.8 TOXICITY TO REPRODUCTION

The potential effects of ethylene inhalation on male and female rat reproduction and on growth and development of the offspring has been studied [70]. The experimental study was carried out according to GLP (OECD Guideline 421; Reproduction/Development Toxicity Screening Test).

Four groups of rats (10 females and 10 males per group) were dosed by head only inhalation for 6 hours daily; air only (control); 200; 1,000 or 5,000 ppm of ethylene (corresponding to 0; 230; 1,150 or 5,750 mg/m^3). This dosing regime was calculated to give about 80; 400 and 2,000 mg/kg/day of ethylene for the three dosed groups respectively. Since the uptake from the lungs most likely is in the range of 5-10 % , the absorbed dose probably was substantially less than the figures given above.

The test material was administered to parent animals for two weeks prior to mating, during the mating period and until the day prior to necropsy for the males (minimum 28 days) and until day 20 of gestation for the females. The females were allowed to litter and rear their offspring to day 4 post-partum, when they and their offspring were killed.

Morbidity, mortality, clinical condition, weight and food intake were observed throughout the study, and mating was carefully observed. For each female, litter data and also observations for each offspring were recorded. At termination of the study, all animals were subject to macroscopic examination for structural or pathological changes. Ovaries, testes and epididymides of the control and high dose animals were subject to a histopathological examination.

There were no deaths attributable to the test article, and body weight gain was not adversely affected during the pre-pairing, gestation or lactation periods. The treatment had no effect on fertility or fecundity and all females became pregnant. Litter size, sex ratio, mean pup weight and pup growth and clinical condition were not adversely affected by treatment.

Necropsy revealed no macroscopic finding suggestive of toxicity due to test article administration. There was no evidence of any toxic effect on the testis due to test substance administration and there were no other microscopic findings suggestive of toxicity due to test article administration.

In conclusion, head-only administration of ethylene at nominal concentrations of 200; 1,000 or 5,000 ppm was without evidence of toxicity or adverse effects on male and female reproductive performance, fertility, pregnancy, maternal and suckling behaviour and growth and development of the offspring from conception to Day 4 post-partum.

5.9 DEVELOPMENTAL TOXICITY/TERATOGENICITY

It is referred to the experimental study [70] carried out according to the OECD Guideline 421; Reproduction/Development Toxicity Screening Test. The study is summarised under point 5.8 above.

5.10 OTHER RELEVANT INFORMATION

A. Specific toxicities (neurotoxicity, immunotoxicity etc.)
No data

B. Toxicodynamics, toxico-kinetics

Cowles, A.L. et al [51], studied the uptake and distribution of four inhalation anaesthetics in dogs. In a series of 21 experiments, 13 large mongrel dogs were ventilated with a constant concentration of ethylene (1.4 % = 12 g/m^3) and three other inhalation anaesthetics. Concentrations of the anaesthetic were measured by gas chromatography in alveolar gas, arterial blood, brain, muscle and central venous blood. The average times necessary for the partial pressure of ethylene to reach 50 % of the inspired partial pressure (1.4 %) were: alveolar gas, <2.0 min; arterial blood, <2.0 min; brain, 3.7 min; muscle, 8.2 min and central venous, 5.2 min.

Biotransformation of ethylene to ethylene oxide

Ehrenberg et. al, 1977 [52] showed that ^{14}C-labelled ethylene was metabolized to ethylene oxide when administered to male CBA mice by inhalation. This metabolism is of significant concern since ethylene oxide is a potent alkylating agent, a carcinogen and a gentoxicant, and hence more toxic than ethylene. The amount of epoxide formed was quantitatively determined from the degree of alkylation of cysteine and histidine residues in haemoglobin.

In a later study from the same laboratory [45], it was shown that ethylene oxide alkylated nucleophilic sites of mouse DNA. Since the ratio between the degree of alkylation of DNA and that of haemoglobin was the same when exposed to ethylene and ethylene oxide, it was concluded that the latter was the reactive intermediate formed from ethylene in vivo. A comparison of the degrees of alkylation obtained per unit exposure of ethylene oxide and ethylene, showed that at low levels of ethylene, about 8% of the inhaled amount was metabolized to ethylene oxide. The rate of ethylene oxidation followed saturation kinetics with increasing ethylene concentration. At 218 ppm ethylene, the oxidation rate was half of the maximal rate (K_m value). It was estimated that the maximal rate of metabolism (V_{max}) of ethylene corresponds to exposure to an air level of 4 ppm of ethylene oxide.

After exposing rats to automotive engine exhaust, Törnqvist et. al., 1988 [53] identified alkylated amino acids in haemoglobin. These resulted from conversion of about 5-10 % of inhaled ethylene and propylene to their respective epoxides which again alkylated the nucleophilic sites in haemoglobin. This quantification of the fraction of ethylene to be oxidised form agreed very well with the conversion factor of around 8 % found for the mouse in the above mentioned study [45].

Results from Törnqvist and Ehrenberg in 1990, estimate that in humans, some 6 % of inhaled ethylene in mainstream smoke is converted to ethylene oxide in smokers [54] and some 3 % in non-smokers [55].

Metabolic conversion of ethylene to ethylene oxide results in the formation of adducts to DNA and proteins, and this offers a means for identifying ethylene exposure in vivo. Determination of haemoglobin adducts using the N-alkyl Edman method has proven valuable [53]. This method has been used for monitoring adduct formation after ethylene exposure from different sources [49].

Toxicity of ethylene oxide

Ethylene oxide causes dose-related increases in the incidence of gliomas, peritoneal mesotheliomas and mononuclear cell leukemias in F 344 rats and lymphomas and adenomas/adenocarcinomas of the lung, uterus, harderian gland and mammary gland in B6C3F1 mice (for a review see Walker et. al., 1990 [56]).

Epidemiologic data on ethylene oxide support the anticipation that ethylene oxide is a carcinogenic agent. When mortality and incidence of cancer in totally 733 workers exposed to

ethylene oxide were assessed, 8 cases of leukaemia and 6 cases of stomach cancer occurred, while the expected numbers were 0.8 and 0.65 respectively [57].

In vivo as well as in vitro, ethylene oxide is seen to react both with amino acid residues in proteins and with the purine bases in DNA. When mouse, human or rat erythrocytes were exposed to ethylene oxide, the main reaction products with haemoglobin were 2-hydroxyethylations of cysteines, N-terminal valine, imidazole nitrogens of histidines and carboxylic groups [58]. The main reaction product after reaction with calf thymus DNA was N-7-(2-hydroxyethyl) guanine, whereas O-6-(2-hydroxyethyl)guanine was only about 0.5 % of this. Species differences were also observed, as rat and mouse erythrocytes were more susceptible to alkylation than the human erythrocytes.

The alkylation of DNA-bases with ethylene oxide has been studied further after exposure of rats to ethylene oxide by inhalation [59, 56, 60]. The main alkylation site both in vivo and in vitro is the N-7 position in guanine, resulting in 7-(2-hydroxyethyl) guanine, and this modification is probably the reason for its carcinogenic and mutagenic effects.

The IARC working group evaluated ethylene oxide in 1994 and came to the overall conclusion that it was carcinogenic to humans [61]. This was mainly based on the evidence for carcinogenicity from experimental studies in animals.

Effects of PCB-pre-treatment on ethylene toxicity and biotransformation

It has been demonstrated that ethylene, as well as halogenated ethylenes are acute hepatotoxic in rats pretreated with polychlorinated biphenyl (PCB) [62]. The hepatotoxicity was evident as increased serum alanine-α-ketoglutarate transaminase (SAKT) and sorbitol dehydrogenase (SDH) in rats pretreated with PCB and exposed to 20,000 ppm ethylene for 4 hours. Without pretreatment with PCB, ethylene and halogenated ethylenes are not acute toxic. From these findings it was suggested that the acute toxicity was mediated through epoxide intermediates formed by hepatic mixed function oxidases induced by the PCB pre-treatment.

When rats were exposed to ethylene in a closed desiccator jar chamber, the rate of metabolic elimination of the compound is influenced by pretreatment with PCB (single dose of Aroclor 1254, 500 mg/kg in oil 6 days prior to the experiment) [63]. Biotransformation of ethylene lead to ethylene oxide which was exhaled.

The effects of PCB pre-treatment and high exposure levels of ethylene, due to induction of mono-oxygenases and increased formation of ethylene oxide, demonstrates that the toxicity of ethylene is of concern for organisms also exposed to mono-oxygenase inducers. However, it should be kept in mind that the concentrations used are far above actual exposure levels.

5.11 EXPERIENCE WITH HUMAN EXPOSURE

Ethylene was in general use as an anaesthetic for many years. It has been replaced by more modern anaesthetics, mostly due to the high explosion risk. Chronic injury in humans resulting from prolonged and repeated exposure to low concentrations of ethylene (less than 2.5 %) was not reported in "Patty's Industrial Hygiene and Toxicology (1981)" [11].

Inhalation pharmacokinetics

The inhalation of ethylene was investigated in human volunteers at atmospheric concentrations of up to 50 ppm. The uptake, exhalation and metabolism could be described by first-order kinetics [64]. The clearance due to uptake was low, only 5.6 %, while the rest was exhaled without entering the blood stream. Clearance due to metabolism was 36 % of systemic available ethylene. The biological half-life of ethylene was 0.65 hours. The alveolar retention of ethylene at steady

state was calculated to be 2 %. The low uptake rate of ethylene was considered due to its low solubility in blood.

Reproduction effects
In a preliminary study, the miscarriage rate (six out of 15 pregnancies) amongst Swedish women who had worked in the local petrochemical industry was higher than that seen in 1549 women outside the industry. Ethylene was the main product in four of the five local petrochemical plants. No data were provided on occupational levels but measurements made in areas surrounding the plants indicated that ethylene was present in concentrations up to tenfold higher than the other pollutants (propylene, ethane, propane and phenol) [65].

A brief abstract notes that there was a higher than expected rate of miscarriage and gynaecological disease among female operatives of a polyethylene plant who were exposed to ethylene concentrations in the range of about 40-60 ppm and high levels of noise [66].

Carcinogenicity
A preliminary study found no increase in lung cancer incidence in 31 workers exposed to ethylene (at unspecified levels) at a US petrochemical factory [67].

A study of workers at an US petrochemical plant found that an increased risk of developing brain cancer was associated with exposure to (unspecified levels of) a number of chemicals including ethylene. However, the investigators were unconvinced that the association reflected a casual relationship [68].

Work Place Exposure
Personal and stationary monitoring of ethylene in a company where this gas was used for controlling the ripening of bananas showed air concentrations to be in the range of 0.02-3.35 ppm (0.02 - 3.85 mg/m^3), with an estimated average concentration of 0.3 ppm (0.35 mg/m^3). In a study on exposure of fire-fighters, samples taken during the "knockdown" phase of a fire showed a concentration of 46 ppm (53 mg/m^3) ethylene, while none was detected during the "overhaul" phase [3]

A study was carried out among workers at a Swedish petrochemical plant using measurements of haemoglobin adducts formed from ethylene oxide for monitoring of ethylene exposure [69]. The study was carried out in two parts, part one in 1989 and part two in 1993. Eight workers exposed to high levels of ethylene (4 mg/m^3) and 3 workers exposed to low levels (0.1 -0.3 mg/m^3) were compared to nine controls exposed to 0.01 mg/m^3. All exposed workers showed elevated levels of haemoglobin adducts and adduct formation was dose-related. The results indicated that about 1 % of the inhaled ethylene was metabolized to ethylene oxide.

The second part of the study, which included four workers, was designed to more accurately determine the exposure levels, which turned out to have a mean of 4.5 mg/m^3. The results confirmed part one, showing that about 1 % of inhaled ethylene was metabolized to ethylene oxide and the maximum fraction to be converted was estimated to be 4 %.

The peak level of ethylene reported for human exposure is about 50 ppm (57.5 mg/m^3), while 3.5 ppm (4.0 mg/m^3) has been characterized as a high average level for longer term exposure. The conversion will then correspond to maximum 2 ppm (3.6 mg/m$^{3)}$ of ethylene oxide for the peak level and to maximum 0.14 ppm (0.25 mg/m^3) for the high averaged level. Given occupational exposure limit levels for ethylene oxide (time-weighted averages) are 1.8 mg/m^3 (Denmark, Japan, USA, Norway) and 2.0 mg/m^3 (France, Canada, Sweden) [3].

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SIDS　エチレン評価文書

OECD からの HPV 化学物質に関する利用可能なデータの要求に対する回答の要約

SIDS プロファイル

1.01A	CAS NO.	
1.01C	化学名	
1.01G	分子式	
	その他の化学的性質情報	
1.5	量	数百万トン／年（1996 年生産量） ノルウェー：0.4 世界：83.0
1.7	利用パターン	化学工業;化学薬品、石油化学製品および樹脂の合成用原料として。 少量は果実の成熟、および麻酔薬ガスとして使用される。
1.9	曝露源	燃料、石炭およびガス燃焼。 化学工業からの漏出。 田園地帯:<1 - 5mg/m3(0.9 -4.3ppb) 渋滞エリア:1.0mg/m3(0.9ppm)以内 石油化学プラント:5mg/m3(4.3ppm)以内
議論のための出版物(もしあれば同一性)	さらなる試験を要しない。	

1. 一般情報

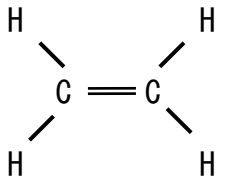
A. CAS number: 74-85-1

B. Name (IUPAC): エチレン

C. Name (OECD): エチレン

F. 分子式: CH_2CH_2

G. 構造式:



H. 物質グループ: 産業化学薬品;化学薬品、石油化学製品および樹脂の合成用原料として。

J. 分子量: 28.05

1.02 OECD 情報

A. スポンサー国: ノルウェー

B. 指導組織:

ノルウェー汚染管理局 (SFT),
P.O. Box 8100 Dep.,
N-0032 Oslo
NORWAY

Contact person:

Marit Kopangen
Tel.: +47 22 573400
Fax.: +47 22 676706

C. Name of responder:

Noretyl ANS,
Petrochemical division,
Norsk Hydro ANS,
N-0240 Oslo
NORWAY

1.1 一般的な物質情報

A. 物質のタイプ: 有機物, 炭化水素

B. 物理的形状 (20℃、1.013hPaにおいて): 気体

C. 純度:

1) 高純度: > 99.9 %

2) 商業的純度 : 約 99.9 %

1.2 同意語

Ethene, acetene, bicarburetted hydrogen, olefiant gas, elayl.

1.3不純物

西ヨーロッパ製, (ppm range):

Methane + ethane (50-200), propylene and heavier (7-200), CO2 (2.2-50), H2(0.1-10), O2 (0.6-10), acetylene (1.4-10), total sulphur (1-10), water (0.6-20) and CO (0.15-10) [3].

1.4 添加剤

知られていない

1.5 生産量

年間1,000,000 トン以上

1996年の生産 [2]:

ノルウェー: 405,000 トン

世界: 83,000,000 トン

1.6 表示と分類

EEC: Fx, R12 (非常に可燃性).

S 2 (子どもの手の届かない場所).

S 9 (よく換気された場所に容器で保存)

S 16 (発火源から離しておくー禁煙)

S 33 (静電気放電に対して予防策をとる)

Norway: F, R13 (非常に可燃性の液体ガス)

S 9-16-33

IARC モノグラフ Volume 60, (1994)による:

Ethylene:人間に対する発癌性物質には分類されていない。[3].

1.7 用途

エチレンは、世界中の大多数で石油製品として生産されている。現在、エチレンの

毎年の商業生産の95%以上は石油の炭化水素のスチームクラッキング(無触媒水蒸気改質）によっている[4]。

米国、西欧、および日本で消費されたエチレンの約80%は酸化エチレン、二塩化エチレン、低密度、直鎖状低密度、および高密度ポリエチレンの生産に使用されている。 また、かなりの量は、エチルベンゼン、アルコール、オレフィン、アセトアルデヒド、およびビニルアセテートを作るのに使用されている。これらの製品の大部分はさらにフィルムや、吹き出し、射出成形や、押出コーティングや、ケーブル絶縁やPVCなどの製品に加工される。 少量が麻酔薬のガス、果実の熟成と金属の溶接と切断に使用されている。

A. 一般

	利用形態：	**カテゴリー：**
a)	主	閉鎖系における利用
	産業	化学工業： 合成に利用
	利用	原材料
b)	主	非分散的利用
	産業	農産業
	利用	果実熟成剤として

B. 消費者向け製品

知られていない

1.8 職業上の曝露限界

被曝限界はほとんどの国で勧告されていないが、スイスでは時間加重平均による職業的被曝限界を11 500mg/m^{3}と制定した。

1.9 曝露源

エチレンは自然および人工を発生源として環境中のどこにでもある。主たる発生源は全てのタイプの植物からの自然の産物である[5]。

主な人為的発生源はガス、石油、石炭、およびバイオマスの燃焼による。人に対するエチレンの最大の曝露は自動車による化石燃料の燃焼を通してと考えられている。地球上の総エチレン排出量は18-45.10^6 t/yであり、うち約74%は自然源、26%は人為的発生源から放出されていると見積もられている。石油の燃焼からの排出量は1.54 .10^6 t/y [5]と推定される。化学産業で生産されて消費されるエチレンは、

閉鎖システム内に保たれており、通常、生産施設はエチレンを原材料として使用している工場に隣接している。その結果、産業からのエチレンの曝露は主に制御できない漏出か破裂によるものである。そのような出来事は年間２百万トンのエチレン製造につき一度の割合で起き、約１トンの直接放出の結果となるかも知れない。

1.10　追加の特記事項

A.　処分に対するオプション

焼却

B.　その他の注意

データ無し

2.　物理化学データ

2.1　融点

-169.15 °C [4]

2.2　沸点

-103.71 °C [4]

2.3 密度

d = 0.57 g/cm3　　沸騰点下 [4].

ガス密度　STP 1.2603 g/l [4].

空気比密度 0.9686 [4].

2.4　蒸気圧

4.27 MPa　　at　　0 °C [4].

2.5　分配係数$\log_{10}P_{ow}$

$Log_{10}\,P_{ow}$ = 1.13 (calculated) [6].

2.6　水溶性

A.　溶解度

メルクインデックスによると,"０℃においてエチレンガスは４倍量の水に溶ける" [7]。25℃では９倍量の水に溶ける。[8].

溶解度：　131 mg/l　20°C　[9]

200 mg/l　15 °C　[10].

B.　水素イオン指数 pH 価,　　酸解離定数 **pKa 価**

有効なデータ無し。溶解したエチレンと水との間の反応およびpHが残って変化しないことを示唆する化学的証拠はない。

2.7　引火点

- 136.11 °C [11].

2.8　自然発火性

自然発火温度：　543°C [7].

点火温度：　425-527°C [4].

2.9　引火性

強燃性－液化ガス.

2.10　爆発性

空気中における爆発限界：　(0.1 MPa and 20$_{o}$C) [4] :

下限爆発限界 (LEL): 2.75 vol %

上限爆発限界 (UEL): 28.6 vol %

2.11　酸化特性

情報無し

2.12　酸化：還元電位

情報無し

2.13　追加データ

A.　土壌／沈殿物と水との間の分配係数　(Kd).

情報無し

B.　その他のデータ

空気中のエチレンに対する換算要素：

1 ppm in air = 1.15 mg/m$_{3}$ = 912 nl/l [1,4]

臭い閾値:

臭いの下限：　299 mg/m$_{3}$

臭いの上限： 4600 mg/m3 [12]

3. 環境中運命および経路

3.1 安定性

3.1.1 空気中安定性

自然および人為起源の大気中エチレンの運命は沢田と戸塚によって1986年に推定された[5]。89%は対流圏においてOHラジカルと反応して、８%はオゾンとの反応によって破壊されたと彼等は結論した。残りの３%は成層圏に運ばれた。エチレンの大気中の寿命は２～４日間と推定された。

増感剤としてオゾンを用いた光分解性による間接的な計算では、9.4日間の寿命であった。OHラジカルを用いた場合は2.7日と算出された。以下の寿命はHoward, P.H. らの (1991) [15] 環境的分解率ハンドブックによるものである。

		寿命
空気：	高	3.36日
	低	0.37日

これはOHとオゾンに対して測定された光分解率に基づいている。
もしAtkinson, R. (1996) [75]による大気中の有機化合物に対する計算手順が使用されるなら、以下の減少率が認められる。

		寿命
空気：	OHに帰する反応	1.7日
	オゾンに帰する反応	10日
	成層圏への移動	1900日

成層圏へのエチレンへの移動がCOと同じと仮定すれば、IPPC (1995) [76]の方法によって計算できる。

3.1.2 水中における安定性

有効なデータはない。

3.1.3 土壌中における安定性

有効なデータはない。

3.2 監視データ（環境中）

Rudolph and Johnen, [16] は、1987年にプエルト・マドリン(アルゼンチン)からブレ

ーマーハーベン (ドイツ)までの航海中に、200以上の場所でエチレンとその他の選択された大気中炭化水素成分を測定した。測定場所は周辺に生物活動が少ない遠い海域であった。混合率で表されたエチレンのレベルは南半球では10-30 ppt (12-35 ng/m3)の範囲であり、北半球では２倍であった。観測されたエチレン値は主として海洋放出の結果であり、示された差は海洋性植物プランクトンの集まり方の変化によって引き起こされていた。

エチレンとその他の低分子炭化水素（ＬMW）の海洋における分布はSwinnerton and Lamontagne, 1974 [17] によって調べられた。彼等は遠洋および沿海から452の海水サンプルから低分子炭化水素を分析し、エチレンの平均的な基準値は4.8 nanoliters/litre (6.0 µg/l)であることを発見した。高い方の値は、ミシシッピのR.. Deltaの35.0 nl/l (44 µg/l)およびマイアミのドック側の地域の30.0 nl/l (38 µg/l)であった。

燃料、石炭、ガスの燃焼、化学産業からの漏出。農村：< 1 - 5 µg/m3、交通量の多い地域：1.0 mg/m3 まで[1, 3]

森林（モミ）火災の時に煙の中から約50 ml/m3 (63 mg/m3）の濃度のエチレンが計測された。

3.3 推定環境濃度を含む環境区画間の移動と分布および分布経路

沢田と戸塚[5]による大気中のエチレンの動態に関する研究では、以下のようなエチレン（in 10^6 t/y）の排出が推定された。

自然：		
陸上	23.3	（65.8%）
水中	2.9	（8.2%）
計	26.2	（74.0%）
人為：		
石油燃焼	1.5	（4.28%）
石炭燃焼	0.42	（1.20%）
工場からの漏出	0.03	（0.09%）
焼却	0.10	（0.29%）
山火事	7.10	（20.1%）
計	9.19	（26.0%）

分布経路合計　自然＋人為＝35.4*10$_6$ t/y

エチレンの大気中の減少

エチレンはOHラジカルと反応して、酸素と窒素酸化物があればフォルムアルデヒドを形成する付加体を作る。エチレンとオゾンの反応による産物はほとんど一酸化炭素、二酸化炭素、水およびフォルムアルデヒドである[76]。いくらかの量のエチレンは成層圏へも移動している。最新の推定による大気中のエチレンの減少率（寿命）は以下のプロセスのようである。

	寿命（日）
OHラジカルとの反応	1.7
オゾンとの反応	10
成層圏へ	1900
大気中における合計寿命	1.45

エチレン（移動容量、10$_6$ tons/y)	
OHラジカルとの反応	44.4（85.4%）
オゾンとの反応	7.5（14.5%）
成層圏へ	0.036（0.07）
計	52.0

成層圏へ移動するエチレンは結局はオゾンと反応してkrüger分子を産生し、それはふたたび一酸化窒素と反応してオゾンを再生するかもしれないので、エチレンは潜在的なオゾンの破壊者としては疑われない。

3.3.1 移動

エチレンの物理的性質は、それがどんなタイプの解放においても大気中に急速に移動するであろうことを示唆している。

3.3.2 理論的分配 (逃散能計算)

６区画モデル(空気、水、固体土壌、沈殿土壌、浮遊土砂および魚)を使用した逃散能レベルⅠの計算が、OECDの世界的な参考モデルを用いて行われた[19]。環境変数としてのデフォルト値は変えられなかった。 入力された一般的な変数は以下の通りである: 融点－169.15℃、蒸気圧は4.27メガパスカル、水への溶解性は200g/m3、分配係数のlog10POWは1.13、空気中の半減期56時間、水、固体土壌、沈殿土壌での半減期は672時間であった。このことは以下の分配を与えた：

空気中	99.99915 %,
水中	$8.27.10^{-4}$ %,
固体土壌中	$9.88.10^{-6}$ %
沈殿土壌中	$2.20.10^{-7}$ %.
浮遊物中	$6.87.10^{-9}$ %
魚類中	$5.58.10^{-10}$ %

このことは、すべての実用的な目的において、放出されたエチレンは空気中だけに分配されることを意味している。

3.4 実際の使用での分解性の主なモードの識別

3.3を参照

3.5 生分解

数多くの関連した調査研究は、土壌や淡水系またはその他の自然系や純粋培養から分離された微生物による、様々な炭化水素の酸化／ヒドロキシル化反応とエポキシ化を調べるように設計されていた。一般的に、これらの研究の結果は、エチレンは様々な微生物で生物分解を受けることがあるのを示しており、酸化エチレンとエチレン・グリコールはたぶん初期の分解産物である[21]。

水の微生物分解速度は、有酸素と嫌気性の両方の状態で見積もられている[15]：

有酸素半減期：	高：	672 時間
	低：	24 時間
無酸素半減期：	高：	2688 時間
	低：	96 時間

3.6 BOD_5, COD または BOD_5/COD比

役立つデータはない。

3.7 生物蓄積性

エチレンは$Log_{10} P_{ow} = 1.13$であるために生物蓄積性は期待されていない。

BCF（生物濃縮係数）は淡水魚ファットヘッド・ミノウ (pimephales promelas)において無極性分子の毒性作用に基づき4になるように計算された(QSAR : 定量的構造活性相関)、露出持続時間2.00－304日間であった[22]。

3.8　追加の特記事項

無し

4.　生態毒性データ

4.1　魚類への急性毒性

魚類に対するエチレンの急性毒性についてはあまり知られていない。しかし、1963年の“カリフォルニア州水資源管理部の水質基準[23]”は、オレンジスポッティド・サンフィッシュに対するエチレンの毒性についての1917年[24]と1921年[25]の二つの報告を参照している。研究結果は次のようである：

1 時間後の致死濃度：　22 - 25 mg/l [24]

1 時間以上の致死濃度：　22 - 65 mg/l [25]

Ecotoxicity Profile database [26]で計算値（QSAR：定量的構造活性相関）が報告された。

Fathead minnow (*Pimephales promelas*) 4 days LC_{50} 116 mg/l

Bluegill, (*Lepomis macrochirus*) 4 days LC_{50} 85 mg/l

Channel catfish, (*Ictalurus punctatus*) 4 days LC_{50} 50 mg/l

Rainbow trout, Donaldson trout,

(*Onchorhynchus mykiss*) 4 days LC_{50} 55 mg/l

Leeuwen [27]らによって計算値（QSAR：定量的構造活性相関）が報告された

Fathead minnow (Pimephales promelas) 4 days LC_{50} 120 mg/l

4.2　水棲無脊椎動物に対する急性毒性

A.　ミジンコ

Ecotoxicity Profile [26]のデータベースで計算値(QSAR)が報告された。

Water flea, (Daphnia magna) 48 hours LC_{50} 53 mg/l

Leeuwen　ら[27]による計算値は：

Daphnid 48 hours LC_{50} 153 mg/l

B.　その他の水生生物

有効なデータは無い。

4.3　藻類に対する毒性

Selenastrum capricornutum　に対する生長阻害試験が1996年にOECD201による GLP(優良試験所基準)のガイドラインに従って実施された[74]。8.2　から131 mg/l.

の間の５つの設定濃度が培養基においてテストされた。72時間の期間中にエチレンの喪失はあったものの、測定された平均エチレン濃度（0と72時間の測定値の平均）が、生長阻害の計算に用いられた。そのため実際の試験濃度は3.3, 7.8, 13.9, 32 and 58mg/l.であった。培養期間の72時間の間のエチレンの損失は64～91％の範囲であった。対照と比較した生体量の減少に基づく生長阻害に対する半数影響度（EC_{50}）は40 mg/l (95 % conf. lim.36-46 mg/l)であろうと算出された。種特有の成長率に基づいて、0-72時間のEC_{50}は72 mg/lと計算された（95 % conf. lim.はEC_{50}が試験した範囲外であったために計算できなかった）。最も高いNOEC（無影響濃度）は13.9 mg/lであった。その結果は、QSARによる*Selenastrum capricornutum*に対して得られた48時間後のEC_{50}：122.5 mg/l [27]とかなり良く一致した。

4.4 細菌に対する毒性

バクテリア懸濁液の中を10分間一定の速度でガスを通過させるやり方で、*E.coli*細菌を処理した。24時間の曝露後に、懸濁液は寒天培地に塗布されて24時間37℃で培養された。ガス処理された細胞からのコロニーの生存数は対照の79 ±1.3 %であった。同様の処理を受けた*E. coli*のSd-4株の生存数は対照と比較して84.2 ± 1.6%であった。その処理は両方の細菌株の生存に何らかの影響があったとしても軽微であるように思われると結論された[28]。

4.5 水生生物に対する慢性毒性

4.5.1 魚類に対する慢性毒性

Ecotoxicity Profile [26]のデータベースに算定値（QSAR）が報告されている。

ファットヘッド・ミノウ（Pimephales promelas）における32日間の最大許容毒性濃度（MATC）は15.3 mg/lである。

Leeuwen et. al. [27]による算定値（QSAR）は

ファットヘッド・ミノウ（Pimephales promelas）における28日間の無影響度（NOEC）は13 mg/l。

4.5.2 水生無脊椎動物に対する慢性毒性

Leeuwen et. al. [27]による算定値(QSAR) ：

ミジンコにおける16日間の無影響度（NOEC）は 37.4 mg/l

4.6 陸生生物に対する慢性毒性

4.6.1 土壌生物に対する慢性毒性

データ無し

4.6.2 陸生植物に対する慢性毒性

エチレンの曝露と影響について数百の観察結果を含む、維管束植物へのエチレンの影響について多数の種々の文献がある。これは主としてエチレンが、異なる反応の範囲の全体を調節する植物ホルモンとして作用しているという事実による。これらの反応の大部分は、摘花、成熟、伸張の抑制、葉の損失と老齢化のような効果を含む成長調節として分類することができる[9,11, 29, 30, 31, 32]。これらの効果のほとんどは非可逆的である一方、植物の生長と繁殖の適合性を減ずるような影響を全くもたらさない。その影響は適合性、生長または繁殖の減少に関連している長期間の影響と想定されることに基づく３グループに分類されるかもしれない。産業地帯における曝露に関連した危険性についてのより現実的な観点を与えている現在のデータに従って、以下の表では熱帯植物は除かれている。

維管束植物へのエチレン露出の効果の概要表。熱帯植物は含まれていない。
上偏生長（Epinasty）=縮葉、器官脱離（Abcission）=喪失

影響	曝露時間	濃度 μ g. m^{-3}	参照
1) 長期間の影響が無しまたは少			
上偏生長,レモン		25-50	[77]
上偏生長,トマト	3-4 h	46	[9]
上偏生長, アカザ属		60	[9]
上偏生長, じゃがいも	16 h	60	[9]
2) 長期間の影響によるかもしれない効果			
生長抑制, スイートピー, (NOEC)	2 d	12	[77]
花の部分欠如, カーネーション	2d	58	[77]
光合成の阻害. エンドウ (NOEL)	2 h	115	[77]
花の部分欠如, キンギョソウ	1h	575	[33]
3) 長期間の影響:			
花の量の減少, エンバク	100d	8	[77]
生長阻害, ジャガイモ	28 d	27	[77]
収量減少, トマト	28 d	50	[77]
成長遅延, エンドウ		116	[9]
収量減少, コショウソウ (30 %)	14 d	115	[77]
収量減少, ワタ	30 d	700	[9]

農業または園芸作物の中ではエンドウ、ジャガイモ、トマトおよびエンバクがよ

り感受性であり、8-50 µg/m3 (7-40ppb)の範囲の濃度において遅延効果が観察された。最も影響されやすい非木本植物がアフリカン・マリーゴールドの葉の上偏生長反応（1.16 µg/m3 (1.0 ppb)のエチレンで下向きの縮葉[9]、カトレヤに対して24時間のエチレン曝露後に2.3 µg/m3 (2.0 ppb)においてガク片の組織崩壊（花の損失）の反応が報告された。

4.6.3 哺乳動物以外のその他の陸生種に対する毒性（鳥類を含む）

データ無し

4.7 生物学的影響のモニタリング(生物濃縮を含む)

データ無し

4.8 環境種における体内変化と動力学

データ無し

4.9 追加の特記事項

データ無し

5. 毒性

5.1. 急性毒性

5.1.1 急性経口毒性：

関係がない。エチレンは沸点の低いガスである（-103.71 □）

5.1.2 急性吸入毒性

エチレンの急性毒性は低いが、非常に高い濃度は酸素置換による窒息を引き起こすかもしれない。 ネズミに対する空気中の致命的なエチレン濃度は95万ppmであると推定されている[34]。

雄のラットを４時間10, 25 or 57·10^3 ppmに曝露した時、全てのグループが血清中のピルビン酸イオンと肝臓の重量増加を示した。GLP（優良試験所基準）に準拠した研究はなかった。

5.1.3 急性経皮毒性

関係がない。エチレンの脂肪に対する低い溶解性と低い沸点のために、エチレンは皮膚を通して吸収されることはほとんど無いと思われる。

5.1.4 管理の他のルートにおける急性毒性

情報がない

5.2 腐食性／刺激性

5.2.1 皮膚刺激／腐食

液体エチレンが刺激性であることを示唆する証拠はないが、霜害を引き起こすかもしれない。

5.2.2 眼刺激性

液体エチレンが刺激性であることを示唆する証拠はないが、霜害を引き起こすかもしれない。

5.3 皮膚感作性

データ無し

5.4 反復投与毒性

エチレンの毒性が４区の曝露処理と無処理に区分したそれぞれ30頭（雄15、雌15）のラット群について90日間の吸入試験でテストされた[36]。ネズミたちは一日６時間、週に５日間で13週の間曝露された。曝露グループはT-I: 300 ppm, T-II: 1,000 ppm, T-III: 3,000ppm および T-IV: 10,000 ppm.であった。研究はＧＬＰに準拠してはいなかったが、高い科学的規格を保持し、品質を保証する声明書が発行された。無処理と処理されたネズミの間には、総重量、体重変化、食糧消費量、血液学、臨床化学、総計の病理学または組織病理学に関して違いが全くなかった。無処理、T-I および T-IV処理グループの雄ネズミは鼻の周りに赤い付着物または排出物を見せた。一方、T-II グループの雄ネズミは眼の周りに赤い付着物があった。雌の中で一頭のT-I の左目の周囲に赤い付着物が、一頭のT-I の両耳の周囲に脱毛が認められた。対照と比較して曝露処理の幾つかのグループにおいて肝臓重量が有意に低かった。しかしながら、この重量減少は無投与との関係が無く、その原因は不明であった。エチレンは段階的に管理された曝露では10,000ppmまではネズミに毒性はなかった。

試行的な非GLP研究では、6匹の雄のSprague‐Dawley系アルビノ・ラット(50-60g)が６日間、吸入剤として酸素中に60％のエチレンの連続フローに曝露されたグループにおいて、いくつかの血液学パラメタで影響を見ることができ [37]、栓球の数(-19.3%)と白血球数(-48.2%)の有意な減少があった。骨髄細胞においても同じ減少(-30%)が見られた。

新生ラットについて90日間2.62ppmの濃度での曝露(連続吸入)した慢性試験中に、発毛の遅延、歯列状態、開眼と低血圧、コリンエステラーゼ活性阻害、従属分裂が報告された[38]。この研究の質に関する情報はない。

濃度100ppmで70日間の吸入処理されたネズミでは、反射神経刺激における変化、コリンエステラーゼ活性の減少、および血圧の減少が観察された[39]。この研究の質に関する情報はない。

5.5 IN VITRO 遺伝毒性

A. 細菌試験

20%までの空気中濃度のエチレンが、ネズミチフス菌（Salmonella typhimurium）に対して、代謝活性化の添加および無添加のシステム(エームス試験)において突然変異性の兆候を示さなかった[40]。研究はＧＬＰに従って行われておらず、ガイダンスで推奨されている四分の一の細菌供試株(TA 100)しかテストされていない。サルモネラ菌の全範囲について代謝活性化システムを添加および無添加の以前のテストでもネガティブの結果が得られている[41, 42]。エチレンはエシュリキア属大腸菌に遺伝的毒性の活性を全く示さなかった[28]。

B. l in vitro での非細菌試験

染色体へのエチレンの影響が、CHO細胞の複製培養を用いてインビトロの細胞遺伝学的分析で試験された。この研究における方法論はＧＬＰとＯＥＣＤの試験ガイドライン473“遺伝毒性：インビトロの哺乳類遺伝学的試験”に従っている。広範囲な投与量をカバーする狭い間隔で分けられた処理が、ラットに導入されたAroclor1254による代謝活性化(S9)の添加および無添加の両方において実施された。使用した中で最も高いレベルの投与量(約280.5mg/ml)は、10mMの濃度に同等であり、エチレンの約25%に一致している。

空気に混ぜた時の試験品の爆発性のために、搬送ガスとして空気を使用する規定ガイドラインによって、必要な最高濃度を達成することは出来なかった。したがって、高投与量の達成を許容する窒素が搬送ガスとして使用された。しかしながら、窒素大気には連続処理に関連している技術的問題があり、短い周期(3時間)の処理が唯一の実用的な選択肢であった。

CHO細胞へのエチレンの毒性効果を調べるための範囲を見つける予備試験が行われた。この試行において、結果を収める前に17時間の回復期が伴ってのみ、S9の添加および無添加処理が３時間続けられた。主たる研究における投与量レベルは、

分裂指数によるエチレンの影響評価によって、選択された。
距離計（range-finder）を使用した処理工程が主たる研究において繰り返された。染色体の異常は3つの連続した投与量レベルで分析されました。解析で選ばれた最も高い濃度(280.5 µg/ml)において、S9を添加してもしなくても、細胞分裂の阻害（分裂指数の減少）は観察されなかった。また、無処理の対照群は主な研究に含まれていました。

適切なネガティブ(搬送ガス)コントロールがそれぞれの処理状態で両方の実験におけるテスト・システムに含まれていた。ネガティブと無処理の培地における構造的な異常を伴う細胞の割合は、歴史的な溶媒によるコントロールの範囲の中にあった。4-Nitroquinoline 1-oxideとシクロフォスファミドがそれぞれ肝臓S9が添加および無添加の陽性対照物質として使われた。これらを受ける細胞が、主な研究で処理開始の20時間後に抽出され、両方の化合物とも構造に異常のある細胞の割合が統計的に有意な増加を引き起こした。

S9の添加および無添加でのエチレンを伴う培養処理は、構造に異常のある細胞の頻度は同じようであったが、陰性対照に伴って見られたそれとは有意な違いはなかった。処理培地で見られた頻度は正常の範囲内にあった。

Ｓ９の添加および無添加のいずれでも10 mM (25 %)の濃度に曝露されたチャイニーズ・ハムスターの卵巣細胞の培養において、エチレンは染色体異常を引き起こさないと結論された。

5.6 ***IN VIVO*** **遺伝毒性**

ラットとマウスの骨髄細胞における小核形成への影響が、次のエチレン吸入で研究された[43]。の2種それぞれ10匹の動物から成る各グループは、一日６時間、週に５日で４週間の期間に0; 40; 1,000 and 3,000 ppmの濃度が投与された。両種の酸化エチレン対照群が、同じ条件で200ppmの濃度で曝露された。骨髄は最後の曝露の約24時間後に集められた。エチレンはどちらのネズミの骨髄において曝露に関係した小核を有する多染性赤血球の頻度の統計的に有意な増加を産み出さなかった。一方、酸化エチレンの曝露は両種ともに有意な増加であった。その研究がＧＬＰに従って運営されたかどうかは記述されていない。

エチレンの吸収、分配、除去と、ヘモグロビンおよびDNAの付加体の形態が、一日12時間の３日連続した300ppmのエチレンの吸入の後のラットで研究された[44]。DNA付加体の形成は肝臓とリンパ球で測られ、ヘモグロビン付加体は赤血球の中

で測定された。エチレンによる付加体形成は他のアルケン類((二重結合を一つ持つ不飽和脂肪族炭化水素))と比較され、付加体形成の減少は分子中の炭素原子の数が増加することでわかる。この研究はＧＬＰの指針によらない試行的な研究であった。

7ーグアニンのアルキル化は、８時間の初期濃度が11ppmであるときの14C-エチレンに14時間吸入曝露させたマウスの肝臓、脾臓と睾丸からのDNAで測定された。アルキル化の度合いは他の組織よりはるかに肝臓で高かった。 この研究は試行的な非GLP研究であった。

5.7　発がん性

エチレンの潜在的な発癌性はラット（Fischer -344系）を用いた2年間の研究でテストされた。研究は発癌試験のためのOECD ガイドライン451(1981)に先だって行われたが、それでも、研究はいくつかの小さな点を除いてこのガイドラインに従っている。研究では、960匹のラットから無作為に分けられた雌雄それぞれ120匹の４グループが、0(対照); 300; 1,000 ,3,000 ppm に１日６時間、週５日間、24ヶ月間以上にわたって曝露された。

研究期間中､抜け毛と鼻と目の周りのでき物､総体的な眼の異常が観察されたが、異なる処理グループの間に明確な差はなかった。

対照グループと比べてテストグループに組織肥大を示しているネズミの数の総合的な増加があったけれど、この傾向は統計的に有意ではなかった。自然死亡率(15.7%)はすべての処理グループでほぼ等しかった。処理された雄の最終的な体重と総重量の変化は対照グループよりも大きかったが、投与量に関連したパターンは見られなかった。

血液学的、血液化学的および他の調査したパラメタのいずれにおいても処理グループ間に統計的な有意差はなかった。テスト材料の効果に起因する大まかな、または組織病理的な組織の変化も供試されたラットのいずれにも見られなかった。要約は処理による発がん性効果を示すことができる所見がほんのわずかであると報告し、この点についての結論はない。

発がん性の研究からの発表[41]では、結果が「これらの濃度におけるエチレンが慢性の毒性を引き起こす、またはFischer - 344 ラットに対して発がん因子であると

いう証拠はない」との結果を出して結論づけた。しかしながら、、彼らが単完全なレポートの中で説明されている核細胞白血病について議論していないので、後でこの公表と概要は批評された[47]。影響を受けたネズミの数が（90匹のうち）対照グループでは雄が12匹、雌が８匹なのに比べて3,000 ppmを受けたグループでそれぞれ21と11匹に上がっていると主張されていた。他方では、背景としてF344ラットでは単核細胞白血病が75%以上の発生率があるかもしれず、曝露されたネズミにおける更なる増加は人間のがん発生に関して解釈するのが難しいと述べられている。

エチレンの発がん性リスクが1979年に国際がん研究機関(IARC)によって評価された時[1]、動物と人間における物質の発がん性または変異誘発性のワーキンググループには役立つデータが全くなかった。1987年に公表された補足7 [48]では役立つ十分なデータはないと要約されており、エチレンが人間にとって発がん性であると分類できないと述べられていた。IARCワーキンググループ(1994)によるエチレンの最新の評価は、エチレンの発がん性について人間と実験動物では十分な証拠がないと結論した[3]。総合的に見て、エチレンは人間にとって発がん性と分類できないと評価された。生態毒性プロファイルデータベースではQSARシステムにおいて、この化学物質が潜在的な発がん性または突然変異誘発要因であることを示唆する情報はないと述べられている。

がんの危険因子としてエチレンの別の最近の評価では、それが重要な危険因子であると結論づけられた[49]。この結論は突然変異性と発がん性の双方が示されている酸化エチレンへのエチレンの代謝の観察に基づいていた。エチレンの代謝の飽和があるので、用量反応関係による直線的な仮説をこの場合には適用できない。その結果、動物へ多量に投与した実験における知見からは、人間の曝露レベルに対して推定できない。

エチレンの潜在的発がん性は、BIBRA（British Industrial Biological Research Association） の会報でも総括された。このレビューも、酸化エチレンの代謝産物に基づいて、エチレン吸入の潜在的発がん性リスクの詳細な再考に時宜を得ていると結論している。また、評価はエチレンの明確な産業的制限の必要性の再評価を求めている。

5.8 繁殖への毒性

雄と雌のラットにおける繁殖および子の生長と発育へのエチレン吸入の潜在的影響が研究された[70]。その実験的研究はGLP(OECD Guideline421; 繁殖/発育への毒

性審査テスト)に従って行われた。４グループのラット(1グループあたり匹の雌と10匹の雄)が毎日６時間の頭部だけでの吸入で200; 1,000 or 5,000 ppmのエチレンと、空気だけの投与（0; 230; 1,150 or 5,750 mg/m3に相当）が行われた。この投与制は、投与の３グループに対してそれぞれ80; 400 and 2,000mg/kg/dayを与えるために計算された。肺からの摂取がたぶん5-10%の範囲にあったため、吸収量はたぶん上記の数字より実質的に少なかったであろう。

交配に先立つ２週間、交配期間中、および雄では検死の前日まで(最小28日間)、雌では妊娠の20日目まで、供試物が親ネズミたちに施された。雌は出産と、親子が殺されるまでの分娩後４日間は世話をすることを許された。

病的状態、死亡率、臨床の状態、体重および食物摂取量が研究期間中観察され、また交配が注意深く調べられ。それぞれの雌について、産子数および各子ネズミの測定が記録された。研究の終了時、すべての動物が形態的または病理学的な変化を肉眼で検査された。対照および高投与量動物の卵巣、睾丸、および副睾丸が組織病理学検査を受けた。

テスト品に起因する死亡はなく、交配前、妊娠および授乳期間における体重増加は悪影響を受けなかった。繁殖力や多産性に対して処理の影響はなく、すべての雌が妊娠した。産子数、性比、子ネズミの平均体重、成長および臨床状態は処理による悪影響を受けなかった。

検死は、肉眼による検査がテスト品の投与による毒性を示唆する肉眼的発見がないことを示した。試験物の投与による睾丸への毒性影響に関する証拠はなく、さらに毒性を示唆する顕微鏡的所見もなかった。

結論として、名目上の濃度が200; 1,000 or　5,000 ppmのエチレンの頭部だけの投与は、毒性の証拠または、雄と雌における繁殖行動、繁殖力、妊娠、母と子の行動、および受胎から産後４日目の子の生長と発育への悪影響はなかった。

5.9　発生毒性／催奇形性

それはOECD Guideline421にそって行われた繁殖／発育毒性の選択試験が実験的研究に参照されている。その研究は上記の5.8に要約されている。

5.10　他の関連情報

A.　特異的毒性（神経毒性、免疫毒性など）

データなし

B. 毒力学、毒物動態学

コールズ，A.Lら[51]は犬での４種類の4吸入麻酔薬の摂取と分布を研究した。21の一連の実験では、13頭の大型雑種犬に一定濃度のエチレン(1.4%＝12g/m^3)と他に３種類の吸入麻酔薬を吸入させた。肺胞気、動脈血、脳、筋肉、および中央の静脈血の中の麻酔薬の濃度がガスクロマトグラフィーによって測定された。エチレンの分圧が吸気分圧(1.4%)の50%に達するのに必要な平均時間は以下の通りである： 肺胞気、２分以下、 動脈血　２分以下、 脳、3.7分、筋肉 8.２分、中央の静脈、5.2分

エチレンの酸化エチレンへの生体内変換

エーレンバーグらは1977 [52]、雄のCBAマウスに吸入させた14Cでラベルしたエチレンが酸化エチレンに代謝されたことを示した。酸化エチレンは発癌物質であり遺伝子毒である強力なアルキル化剤(DNAを不可逆修飾する抗悪性腫瘍薬の一群)としてエチレンより毒性が強いので、この代謝はとても重要である。形成されたエポキシドの量はヘモグロビン中に残っているシステインとヒスチジンのアルキル化の度合いから量的に決定された。

同じ実験室における後の研究では[45]、酸化エチレンがマウスのDNAの求核部をアルキル化したことが示された。エチレンと酸化エチレンに曝露された時に、DNAとヘモグロビンのアルキル化の度合いの比率が同じであったので、後者が生体内でエチレンから形成された反応中間物であると結論づけられた。酸化エチレンとエチレンの単位あたりの曝露で得られたアルキル化の度合いの比較は、低レベルのエチレンでは、吸入された量の約8%が酸化エチレンに代謝されたことを示した。エチレン濃度の増加に伴うエチレン酸化の割合は飽和濃度まで続いた。218ppmのエチレンでは、酸化率は最高割合の半分(K_m 値)であった。エチレンの最大限度の代謝速度(Vmax)が空気中濃度4ppmの酸化エチレンへの曝露に対応すると推定された。

Törnqvist ら., 1988 [53]は、自動車エンジンの排気に曝露した後のラットで、ヘモグロビンちゅうにアルキル化されたアミノ酸を確認した。これらは吸入されたエチレンとプロピレンの約5-10%がそれぞれのエポキシドに転換し、さらにヘモグロビンの求核サイトをアルキル化した結果である。約8%の換算率にとてもよく一致していたエチレンの酸化される部分の定量化は、上記の研究の中でのマウスで発見された。Törnqvist とエーレンバーグ1990による結果では、人間では、喫煙家において吸入された主流煙中のエチレンの約6%[54]、非喫煙者で約3%[55]が酸化エ

チレンに変換されると推定された。

エチレンの酸化エチレンへの代謝的変換はDNAとタンパク質付加体の形成をもたらし、これは生体内でエチレン曝露を特定するための手段を提供する。N-アルキル・エドマン法を使用したヘモグロビン付加体の測定は役立つと証明した[53]。この方法は異なるソースからのエチレン曝露後の付加体形成を調べるために用いられた[49]。

酸化エチレンの毒性

酸化エチレンは投与量の増加と関連して、F344ラットでグリオーマ、腹膜悪性中皮腫、単核細胞白血病を、B6C3F1マウスでリンパ腫および肺、子宮、ハーダー腺、乳腺の腺腫/悪性腺腫引き起こす（ウォーカーら、1990によるレビュー1990 [56]）。

酸化エチレンに関する疫学データは酸化エチレンが発がん性作用物であるという予想を支持している。酸化エチレンに曝露された733人の労働者の死亡率と発がん率が調べられた時、それぞれの期待数は0.8と0.65であったが[57]、８例の白血病と６例の胃がんが見つけられた。

生体内と同じく生体外で、酸化エチレンはタンパク質のアミノ酸残基とDNAのプリン塩基の双方に反応しているのが見られる。マウス、人間またはラットの赤血球が酸化エチレンにさらされたとき、主な反応の生成物はヘモグロビンでシステインの2ヒドロキシエチレイション、N-末端バリン、ヒスチジンとカルボキシルグループのイミダゾール窒素であった[58]。仔ウシ胸腺のDNAとの反応の後の主な反応生成物はN7(2-hydroxyethyl)グアニンであったが、O-6(2-hydroxyethyl)のグアニンはこの約0.5%にすぎなかった。
また、ラットとマウスの赤血球がヒトの赤血球よりアルキル化に感受性であったように、種間差が見られた。

酸化エチレンによるDNA 塩基のアルキル化が、吸入によって酸化エチレンに曝露させたラットでさらに研究された[59, 56, 60]。
生体内および生体外ともにおける主なアルキル化部位は7(2-hydroxyethyl)グアニンに由来するグアニンのN-7位置であり、この変更がたぶん発がん性と突然変異的な効果の理由である。

IARC（国際がん研究機関）のワーキンググループは、1994年に酸化エチレンを評価し、人間対して発がん性があるという総体的結論に至った。これは主として動

物に対する発がん性に関する実験的研究からの証拠に基づいていた。

エチレン毒性と体内変化におけるPCBの前処理の効果

ハロゲン化エチレンと同様にエチレンがポリ塩化ビフェニル(PCB)で前処理されたラットに対して急性の肝細胞毒であることが示された[62]。PCBの前処理と2万ppmのエチレンに４時間曝露されたラットにおいて、血清のアラニン・α・ケトグルタル酸塩トランスアミナーゼ(SAKT)とソルビトール脱水素酵素(SDH)の増加で肝毒性は明白であった。PCBの前処理がなければ、エチレンとハロゲン化エチレンは急性毒ではない。これらの発見から、急性毒性がPCBの前処理で引き起こされた肝臓の混合機能酸化酵素によって形成されたエポキシドの仲介を通して成立していることが示唆された。

ラットが閉じている乾燥機瓶の部屋でエチレンに曝露されたとき、化合物を除去する代謝速度はPCB前処理(実験の6日前にアロクロール125を500mg/kg油に入れて単回投与)によって影響を受ける[63]。エチレンの体内変化は酸化エチレンとなって放出された。

PCBプレ処理と高い被ばくレベルのエチレンの影響は、モノオキシゲナーゼの誘導と酸化エチレン形成の増加のために、モノオキシゲナーゼ誘導酸素に曝露された生物にとって､エチレンの毒性が重要であることを示している｡しかしながら、使用された濃度が、実際の被ばくレベルをはるかに超えていることを心に留めておくべきである。

5.11 人のばく露経験

一般的にエチレンは麻酔薬として長年にわたって使用された。たいていはその高い爆発の危険性のために、より近代的な麻酔薬に取り替えられた。低濃度のエチレン（2.5％以下）の長期で反復した曝露の結果としての人における慢性的な障害は「Pattyの産業衛生と毒物学(1981)」の中では報告されなかった[11]。

吸入薬物動態学

エチレンの吸入が人間のボランティアで最大50ppmの大気中濃度で調査された。摂取、発散および代謝は一次反応速度論によって説明できた[64]。摂取による除去はわずか5.6％と低く、残りは血流に入ることなく吐き出された。代謝による除去はシステムで使われたエチレンの36%であった｡エチレンの生物学的半減期は0.65時間だった。肺胞に定常的に留まったエチレンは２％と算出された。エチレンの低い摂取率は血液への低い溶解度のためと考えられた。

繁殖への影響

予備的な研究では、地方の石油化学産業で働いていたスウェーデン人女性における流産率(15回の妊娠のうちの6回)は、産業の外部にいた1549人の女性に見られたそれより高かった。エチレンは5ヶ所の地方石油化学工場のうちの4ヶ所における主な生産物であった。職業レベルで提供されたデータは全くないが、領域を囲っている植物での測定では、エチレンがその他の汚染物質(プロピレン、エタン、プロパンおよびフェノール)よりも10倍高い濃度で存在しているのを示した[65]。

簡潔な要約は、約40-60ppmの範囲のエチレン濃度と高いレベルの雑音に曝露されたポリエチレンプラントの女子工員における流産と婦人科病は期待値よりも高い割合であったことが簡潔な要約で言及された[66]。

発がん性

予備的な研究では､米国の石油化学工場でエチレン(不特定のレベルにおける)に曝露された31人の労働者において肺がん発生の増加を全く見つけなかった[67]。

アメリカの石油化学プラント労働者についての研究で、脳腫瘍を発症する危険性の増加がエチレンを含む多くの化学物質の曝露(不特定のレベル)と関連していることが分かった。しかしながら、研究者はその関連性が偶発的な関係を反映していたと確信してはいなかった[68]。

職場の曝露

バナナの成熟を制御するのに使用されている会社における、個人的で定常的なエチレンの観測は、大気中濃度が0.02-3.35ppm(0.02--3.85mg/m3)の範囲にあり、平均濃度は0.3ppm(0.35mg/m3)であったことを示した。
消防士の曝露に関する研究では、炎の「圧倒的な（knockdown）」様相の間に取られたサンプルは、46ppm(53mg/m3)の濃度のエチレンを示した一方、精密検査（overhaul）の間には検出されなかった[3]。

スウェーデンの石油化学プラントの労働者を対象に、エチレン曝露のモニターのために酸化エチレンから形成されたヘモグロビン付加体の測定をする研究が実施された[69]。研究は1989年のパート1および1993年のパート2の2つのパートで実施された。高いレベルのエチレンに曝露された8人の労働者(4mg/m3)と、低レベルに曝露された3人の労働者(0.1 -0.3mg/m3)が、対照とした0.01mg/m3に曝露された9人と比較された。全ての被ばく労働者がヘモグロビン付加体のレベルを上げ、付加

体形成は投与量に関連していた。結果は、吸入されたエチレンの約1%が酸化エチレンに代謝されたことを示した。

4人の労働者を含んでいた研究の第二部は、より正確に被ばくレベル、平均4.5mg/m3となるに設計された。結果はパート1を追認し、吸入されたエチレンの約1%が酸化エチレンに代謝されて、変換されるべき最大区分が4%であると推定された。

ヒトの曝露関して報告されたエチレンのピーク水準は約50ppm(57.5mg/m3)であり、一方3.5ppm(4.0mg/m3)は、より長い期間の曝露の高位平均値とみなされた。そして、ピーク水準に対しては最大の2ppm(3.6mg/m3)、高位平均値に対しては最大0.14ppm (0.25mg/m3)の酸化エチレンへの変換に対応するであろう。酸化エチレン(時間加重平均)について定められた職業被曝限界水準は、1.8mg/m3(デンマーク、日本、米国、ノルウェー)と2.0mg/m3(フランス、カナダ、スウェーデン)である[3]。

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IRPTC（International Register of Potentially Toxic Chemicals　国際有害化学物質登録制度）の法的なファイルからの抽出

資料　１０

欧州経済共同体理事会指令 91/414：評価報告書に対する最終補遺
エタノールについての補遺－第３巻、付属書Ｂ．７
反応および分解生成物の毒性（エチレンおよび酸化エチレン）
2008 年 10 月　　（抜粋、p.80-139 の部分は省略）

Final addendum to the Draft Assessment Report (DAR)

- public version -

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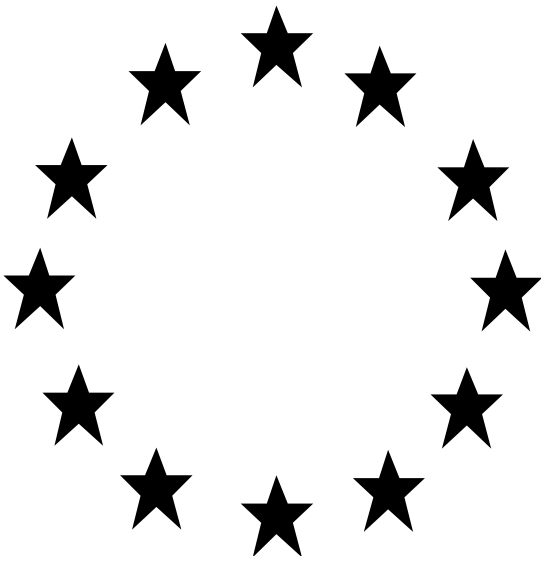

Final addendum to the

Draft Assessment Report (DAR)

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Initial risk assessment provided by the rapporteur Member State The United Kingdom for the Existing active substance

ETHANOL

of the fourth stage of the review programme referred to in Article 8(2) of Council Directive 91/414/EEC

November 2008

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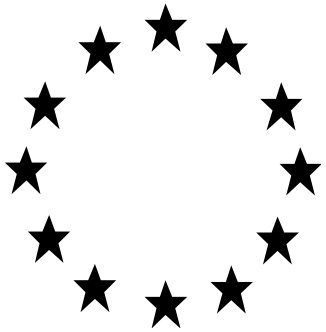


Ethanol

Volume 4

Annex C

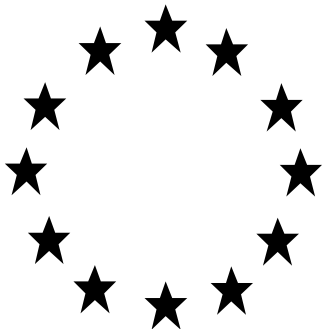
to the Report and Proposed Decision of the United Kingdom made to the European Commission under Article 8(1) of 91/414/EEC

Confidential Information

Draft: August 2008

confidential information available at RMS

Council Directive 91/414/EEC



Ethanol

Addendum 2 to the Report and Proposed Decision of the United Kingdom made to the European Commission under Article 8(1) of 91/414/EEC

Assessment of available information on the toxicology of the reaction and degradation products (ethylene and ethylene oxide)

Note: The sole supported use of ethanol is as a precursor for ethylene. Ethanol is converted to ethylene using a catalytic generator.

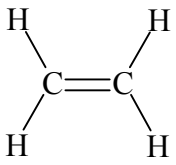
October 2008

B.6 TOXICOLOGY AND METABOLISM

Introduction

Ethylene (or ethene) is the simplest alkene (i.e. an unsaturated hydrocarbon or olefin); it is a very flammable gas and forms explosive mixtures with air. It is an endogenous growth regulator in plants which is used to ripen bananas. The biosynthesis of ethylene in plants is well documented in the literature (Wang *et al*, 2002).

Figure B.6.1 Structure of ethylene



Chemical name: ethylene.
Other names: ethene, acetone, bicarburetted hydrogen and olefiant gas.
CAS Number: 74-85-1.
Molecular weight: 28.05 g/mol.
Molecular shape: planar.
Molecular formula: C_2H_4
Octanol/water partition coefficient: Log Kow = 1.13.
Solubility in water: 131 mg/l at 20ºC.
Vapour pressure: 4.2 x 10^6 Pa.
Physical state: Colourless gas with a slight, sweet and musty odour.
Conversion factors (NTP): i) 1 ppm = 1.15 mg/m^3; ii) 0.86 ppm = 1.0 mg/m^3.

Ethylene is a gas at normal temperature and pressure. It is an asphyxiant and induces hypoxia by reducing the oxygen content of air by dilution.

Ethylene is an important industrial chemical; its uses include the manufacture of polyethylene, ethylene oxide (a fumigant and sterilizing agent), ethylene dichloride, ethylene glycol, linear alcohols, olefins, ethylbenzene, acetaldehyde and vinylacetate. In addition, it is used as a fuel in metal cutting and welding and as an anaesthetic.

Ethylene is ubiquitous in the environment being released into the atmosphere from natural and man made sources. Approximately 75% of the atmospheric ethylene originates from organic sources (e.g. an endogenous growth regulator in plants that is emitted by vegetation and it is produced by micro-organisms as part of their normal metabolism) and 25% from anthropogenic sources (e.g. combustion of gas, fuel, coal and biomass). Atmospheric ethylene can be degraded by ozone (half-life 6.5 days/estimated to destroy 8%), nitrate radicals (half-life 190 days) or by photochemically-produced hydroxyl radicals (half-life 1.9 days/estimated to destroy 89%). The atmospheric lifetime of ethylene has been estimated to be 2-4 days.

Environmental human exposure mainly occurs from the combustion of fossil fuels (e.g. motor vehicle emissions) and the burning of organic matter (e.g. smoking). Ethylene concentrations in ambient air at rural and remote sites are generally in the

range of <0.001-0.005 mg/l and up to 0.05 mg/l in urban and indoor areas (values of up to 1 mg/l have been recorded in heavy traffic). Ethylene is produced endogenously by humans and other mammals and several mechanisms have been proposed for its endogenous production: lipid peroxidation, enzymatic reactions or oxidative destruction of methionione and haemoglobin and by intestinal bacteria.

No metabolism or toxicity studies have been submitted or evaluated for ethylene or its metabolite ethylene oxide (a potent alkylating agent and genotoxic carcinogen). The information and toxicological data cited in this document is entirely dependant on the data cited in the published literature (mainly summarised in the publications listed below). It should be noted that details of the protocols, the dosing patterns and the GLP status of cited studies were minimal and the source, age and quality of the data/information were often unclear and difficult to assess. In addition, no reliable quantitative toxicity data have been submitted for ethylene exposure to experimental animals via the oral route (normally required for determining NOAELs and the setting of reference doses for the consumer risk assessment).

The main publications/sources of information cited in the following ethylene evaluation are as follows:

i) OECD Screening Information Data Set (SIDS): Ethylene. Date not specified. Organisation for Economic Co-operation and Development (OECD: SIDS).

ii) IUCLID Dataset, Ethylene, European Chemicals Bureau, 2000 CD-ROM Edition.

iii) Hazardous Substances Data Bank, No 168, 2003 (HSDB 2003, toxnet.nlm.nih.gov).

iv) IARC Monograph on the Evaluation of Carcinogenic Risks to Humans (1994). Some Industrial chemicals, Vol 60 (Ethylene pages 45-70) (IARC 1994).

v) Proposed Regulatory Decision Document. Ethylene Eco Sprout Guard. Health Canada October 2001 (HC 2001).

Inevitably, the publications listed above are mainly summarising and citing the same studies and data. Since there are minor differences in the reporting of the details by the different sources, individual studies may be cited more than once especially where additional information has been reported. To assist in identifying the studies cited by these publications, the original references (where available) have been cited together with the relevant publication in this evaluation (these references have not been individually evaluated by the RMS). The quality of the studies cited and the extent and depth of the investigations carried out are impossible to ascertain without an extensive evaluation of the individual published studies.

B.6.1 Absorption, distribution, metabolism and excretion (toxicokinetics) (IIA 5.1)

B.6.1.1 Absorption, distribution and excretion

Male Fischer 344 rats (170-220g) were exposed to 14C-ethylene (free of ^{14}C-acetylene or greater than or equal to 97% pure) for 5 hours in a closed chamber (35 litres) to 10000 ppm (11.5 mg/l). In each experiment, up to four rats were exposed together in a single chamber. Within one minute after the end of exposure, animals were transferred to individual all glass metabolism cages and the elimination of radioactivity monitored for up to 36 hours. Most of the eliminated 14C was exhaled as ethylene [(18 µmol (504 µg) per rat exposed to acetylene-containing ethylene; this statement is not consistent with the material tested/no explanation)]; smaller amounts were excreted in urine (2.7 µmol ethylene equivalents/rat) and faeces (0.4 µmol) and exhaled as carbon dioxide. Radioactivity was found in blood (0.022 µmol ethylene equivalents/ml), liver (0.047 µmol ethylene equivalents/liver), gut (0.034 µmol ethylene equivalents/gut) and kidney (0.006 µmol ethylene equivalent/kidney). Pre-treatment of animals with a mixture of polychlorinated biphenyls (Aroclor 1254: 500 mg/kg bw; single intraperitoneal injection 5 days before exposure) had no measurable influence on ethylene exhalation but resulted in a significant ($p< 0.05$) increase in exhaled $14CO_2$ (2.04 µmol ethylene equivalents/rat) and of 14C in urine (11.1 µmol ethylene equivalents/ml). The organ burden of 14C was one to two orders of magnitude greater in Aroclor 1254-treated than in untreated animals. Radioactivity was also detectable in lungs, brain, fat, spleen, heart and skeletal muscle. The data were interpreted as indicating that an inducer of the mixed-function oxidase system can stimulate the metabolism of ethylene.

(Guest *et al*, 1981/IARC 1994)

b) Male Fischer 344 rats (with and without pre-treatment with Aroclor 1254) were exposed to 14C-ethylene (12.56 mg/l= 10000 ppm) for 5 hours. Samples were collected for 36 hr following exposure. Aroclor pre-treatment did not affect the amount of ethylene expired but did cause a 4-fold increase in expired $14CO_2$ and a 2-fold urinary excretion of radioactivity. Aroclor pre-treatment increased the concentrations in blood, gut, kidney, liver and lung by factors of 1.5-, 6-, 8-, 16-, 17-fold; detectable concentrations of radioactivity were also found in brain, heart, fat and muscle. The rats pre-treated with Aroclor showed centrilobular hepatic necrosis (light microscope) which was not seen in the rats exposed to ethylene alone. The author suggested that ethylene metabolism is stimulated by Aroclor treatment.

(Guest *et al*, 1981, IUCLID 2000)

c) Several studies have investigated the pharmacokinetics of inhaled ethylene in male Sprague Dawley rats using closed exposure chambers in which the atmospheric concentration-time course was measured after injection of a single dose into the chamber atmosphere (Bolt *et al*, 1984; Bolt & Filser, 1987; Shen *et al*, 1989; Filser, 1992). Uptake of ethylene into the body was low. Clearance due to uptake (as described above) was 20ml/min for one rat of 250 g which represents only 17% of the alveolar ventilation (117 ml mins; Arms & Travis, 1980). Most (83%) inhaled ethylene that reaches the lungs is exhaled again without becoming systemically available via the blood stream. Maximum accumulation of ethylene in the organism, determined as the thermodynamic partition coefficient, whole body:air (Keq =

$Conc_{animal}/Conc_{air}$), was 0.7. The concentration ratio at steady-state whole body:air was somewhat lower owing to metabolic elimination ad it decreased from 0.7 to 0.54 at exposure concentrations below 92 mg/m^3 (80 ppm). However, at very low atmospheric concentrations, the concentration ratio at steady-state whole body:air increased, owing to endogenous production of ethylene. For instance, it was almost twice the value of the thermodynamic partition coefficient whole body:air at an exposure concentration of 0.06 mg/m^3 (0.05 ppm); calculated using pharmacokinetic parameters and equation 18 of Filser,1992. At concentrations between 92 and 0.12 mg/m^3 (80and 0.1 ppm), clearance was seen, due to metabolism related to the concentration in the atmosphere of about 4.7 ml/min for the 250g rat. In that concentration range at steady state, therefore, about 24% of systemically available ethylene is eliminated by metabolism and 76% by exhalation of the unchanged substance (taking into account values of clearance of uptake and clearance of metabolism). The alveolar retention of ethylene at steady state value was 3.5% and the biological half-life was 4.7 minutes (Filser *et al*, 1992). At atmospheric concentrations greater than 92 mg/m^3 (80 ppm), metabolism of ethylene became increasingly saturated, reaching a maximum rate of metabolism (V_{max}) of 0.035 µmol/(min x 250 g bw) [0.24 mg/(h x kg bw)] at about 1150 mg/m^3 (1000 ppm). The apparent Michaelis constant (k_m) related to the average concentration of ethylene gas within the organism was 130 nl/ml tissue, which corresponds to an atmospheric concentration of 239 mg/m^3 (208 ppm) at $V_{max/2}$, calculated by means of the kinetic parameters given by Filser (1992).

(IARC 1994)

d) In a series of 21 experiments, 13 large mongrel dogs were ventilated with a constant concentration of ethylene (1.4% = 12g/m^3). Concentrations were measured by gas chromatography in alveolar gas, arterial blood, brain, muscle and central venous blood. The average times necessary for the partial pressure of ethylene to reach 50% of the inspired partial pressure (1.4%) were: alveolar gas, <2.0 minutes; arterial blood, <2.0 minutes; brain, 3.7 minutes; muscle, 8.2 minutes and central venous blood, 5.2 minutes.

(Cowles, 1972/OECD: SIDS)

B.6.1.2 Metabolism

A metabolic pathway for the biotransformation of ethylene in mammals was not proposed.

a) Four male CBA mice (average body weight, 31 g) were exposed together for one hour in a closed glass chamber (5.6 litre) to 14C-ethylene (22 mCi/mmol) in air at 17 ppm (0.0223 mg/l) which is equivalent to about 1 mg/kg bw. Blood and organs from two mice were pooled 4 hours after the end of exposure. Radioactivity was about the same in kidney (0.16 µCi/ g) and liver (0.14 µCi/ g) but lower in testis (0.035 µCi/ g), brain (0.02 µCi/ g) and haemoglobin (0.0094 µCi/G Hb). Urine was collected from the two other mice during the 48 hour period and blood was collected after 21 days. A urinary metabolite, 5-(2-hydroxyethyl)cysteine was identified by thin-layer chromatography (3% of 14C in urine). The radioactivity in haemoglobin was 0.011 µCi/g Hb. This data, together with those on specific hydroxyethyl derivatives at amino acid residues of haemoglobin indicates that ethylene was metabolised to ethylene oxide.

(Ehrenberg *et al*, 1977/IARC 1994)

In liver microsomes prepared for male Sprague-Dawley rats, ethylene at concentrations of up to 115 g/m^3 (10%) in the gas phase was metabolized to ethylene oxide in the presence of an NADPH regenerating system (1 hour, pH 7.5, 37ºC). The rate of formation of ethylene oxide was saturable (V_{max} 0.67 nmol/h per mg protein) and could be reduced by the addition of diethyldithiocarbonate or β-naphthoflavone to the microsomal suspension. Treatment of rats with phenobarbital (single intraperitoneal injection of 80 mg/kg bw followed by three days of 0.1% in drinking water) before preparation of liver microsomes did not change the V_{max}.

(Schmiedel *et al*, 1983/IARC 1994)

b) In mice, it was shown that ethylene oxide alkylated nucleophilic sites of DNA in liver, spleen and testes. Since the ratio between the degree of alkylation of DNA and that of haemoglobin was the same when exposed to ethylene and ethylene oxide, it was concluded that ethylene oxide was an *in vivo* reactive intermediate formed from ethylene. A comparison of the degrees of alkylation obtained per unit exposure of ethylene oxide and ethylene showed that at low levels of ethylene, about 8% of the inhaled amount was metabolised to ethylene oxide. The rate of ethylene oxidation followed saturation kinetics with increasing concentration. At 218 ppm ethylene, the oxidation rate was half of the maximal rate (k_m value). It was estimated that the maximal rate of metabolism (V_{max}) of ethylene corresponds to exposure to an air level of 4 ppm of ethylene oxide.

(Segerback, 1983/OECD:SIDS)

c) Involvement of cytochrome P450-dependent monooxygenases in the metabolism of ethylene in male Sprague-Dawley rats was suggested by the complete inhibition of metabolic elimination after intraperitoneal treatment with 200 mg/kg diethyldithiocarbonate 15 min before exposure and by an increase in the rate of its metabolism with a V_{max} of about 14 µmol/(h x kg bw) [0.33 mg/(h x kg bw)] after treatment with a single dose of Aroclor 1254 (500 mg/kg bw) six days before the experiment.

(Bolt *et al*, 1984/IARC 1994)

d) Male Sprague-Dawley rats exposed to ethylene exhaled ethylene oxide. In these experiments, two animals were kept together up to 21 hours in a closed chamber (6.4 litres). The concentration of ethylene in the atmosphere of the chamber was maintained at greater than 1115 mg/m^3 (1000 ppm) by repeated additions, in order to maintain V_{max}. conditions for ethylene. One hour after the beginning of exposure, the atmospheric concentration of exhaled ethylene oxide reached a peak value of 0.69 mg/m^3 (0.6 ppm). After about 2.5 hours, the concentration had decreased to about of 0.345 mg/m^3 (0.3 ppm) and then remained constant. On the basis of the concentration- courses of atmospheric ethylene, it was speculated that this decease was due to rapid induction of ethylene oxide metabolizing enzymes, whereas the rate of ethylene metabolism remained unaffected (Filser and Bolt, 1984). In male Sprague-Dawley rats exposed to ethylene at concentrations greater than 1115 mg/m^3 (1000 ppm), the amount of ethylene taken up per unit time from the atmosphere of a closed chamber remained constant over exposure times of up to 30 hours (Bolt *et al*, 1984). Pharmacokinetic data for ethylene and ethylene oxide indicate that in steady state conditions only 29% of metabolised ethylene is available systemically as ethylene

oxide. Therefore, assuming that the liver is the principle organ in which ethylene is metabolised, an intrahepatic first-pass effect for the intermediate ethylene oxide was suggested (Filser and Bolt, 1984). In view of the saturability of ethylene metabolism, the maximal possible average body concentration of its metabolite, ethylene oxide, was calculated to be 0.34 nmol/ml tissue [15 µg/kg bw] in an open exposure system (infinitely large atmospheric volume). The same value was computed to result from exposure to ethylene oxide at an atmospheric concentration of 10.2 mg/m^3 (5.6 ppm) at steady state (Bolt and Filser, 1987).

(IARC 1994)

e) Metabolic conversion of ethylene oxide results in the formation of DNA and haemoglobin adducts that can be used to identify ethylene exposure. Alkylated amino acids in haemoglobin have been shown in rats exposed to automotive engine exhaust. These adducts resulted from the conversion of 5-10% of inhaled ethylene.

(Tornqvist *et al*, 1988/OECD:SIDS)

f) Ethylene oxide was found in the blood of male Fisher 344 rats during exposure to an atmospheric ethylene concentration of 690 mg/m^3 (600 ppm). A maximal value of about 3µg/g blood of ethylene oxide was seen 8 minutes after the start of exposure to ethylene; this value was followed 4 minutes later by an immediate decrease to about 0.6 µg/g blood and this level remained constant for the following 46 minutes. During exposure, "the cytochrome P450 content in the liver was reduced to 94% after 20 minutes and 68% after 360 minutes" (no further details). It was speculated that an ethylene-specific cytochrome P450 isozyme was rapidly deactivated during exposure to ethylene, resulting in reduced formation of ethylene oxide (Maples & Dahl, 1993). This speculation is based on results obtained by an unspecific method for the determination of cytochrome P450 isozyme which is not suitable for the determination of cytochrome P450 isozymes.

(IARC 1994)

g) In male Sprague Dawley rats treated with phenobarbital (intraperitoneal injection of 80 mg/kg bw/day for 4 days and exposure to ethylene on day 5) and then exposed for 3 hours to a mixture of commercial ethylene (contaminated with about 10 ppm acetylene) and air (1:1 v/v), a green pigment was formed in the liver 4 hours after exposure. The same pigment was formed *in vitro* during incubation of acetylene-free ethylene with 9000 x g supernatant of a rat liver homogenate (from phenobarbital-pre-treated animals) in the presence of NADPH. No controls were used (Ortz de Montellano & Mico, 1980). The pigment was identified as a N-(2-hydroxyethyl)protoporphyrin IX, an alkylation product of the prosthetic haem of cytochrome P450-dependent monooxygenases. It was conclude that the phenobarbital-inducible form of cytochrome P450 was destroyed during oxidative metabolism of ethylene (Ortz de Montellano *et al*, 1980 & 1981).

(IARC 1994)

h) Ethylene oxide is exhaled by untreated rats (Shen *et al*, 1989). The endogenous production rate in a Sprague-Dawley rat (250g bw) was determined to be 2.8 nmol/h [0.31 µg/(h x kg bw)] resulting in a body burden of ethylene gas of 0.32 nl/ml tissue [0.036 µg/kg bw] (Filser, 1992). The corresponding exhalation rate may be calculated from the pharmacokinetic parameters of Filser (1992) as 0.24µg/(h x kg bw). Four

possible sources of endogenous ethylene have been suggested in the literature: lipid peroxidation (Kautiainen *et al*, 1991), enzyme- copper- or iron-mediated catalysed oxidation destruction of methionine (Fu *et al*, 1979; Lieberman *et al*, 1965; Kessler & Remmer, 1990; respectively), oxidation of haemoglobin (Clemens *et al*, 1983) and the metabolism of intestinal bacteria (Tornqvist *et al*, 1989b).

(IARC 1994)

It has been demonstrated that ethylene and halogenated ethylenes are acute liver toxins in rats pre-treated with polychlorinated biphenyl (PCB). Without pre-treatment with PCB and exposed to 20000 ppm ethylene for 4 hours, ethylene and halogenated ethylenes did not induce liver toxicity. The rate of metabolic elimination of ethylene is influenced by pre-treatment with PCB and leads to an increase in exhaled ethylene oxide.

(Conelly and Jaeger, 1977; Filser and Bolt, 1983/OECD: SIDS)

B.6.1.3 Summary of toxicokinetics studies

No ADME studies have been submitted (no oral ADME studies have been cited). The majority of the available data has been generated using inhalation exposure. A metabolic pathway has not been proposed for ethylene in mammals. Apart from ethylene oxide and its metabolites and the urinary metabolite hydroxyethyl cysteine in mice, there appears to be little or no information or investigations into other potential metabolites of ethylene (see B.6.8.1).

Following inhalation of radiolabelled ethylene, absorption appeared to be rapid (within minutes) but the systemic uptake from the lungs was low (low solubility in blood). The uptake, exhalation and metabolism can be described by first-order kinetics. It has been estimated that approximately 83% of the ethylene that reaches the lungs is exhaled unchanged while 17% is absorbed. Distribution is widespread throughout the body (i.e. nervous system, lungs, liver, kidneys, spleen, heart, blood, fat, skeletal muscle and testes). In rats, about 24-29% of systemically available ethylene is eliminated by metabolism and the remainder by exhalation of the unchanged substance. Elimination appears to be rapid. Most of the inhaled ethylene was exhaled unchanged with smaller amounts excreted in urine and faeces and as exhaled carbon dioxide. Pre-treatment with cytochrome P450 inducers increased the amount of $^{14}CO_2$ exhaled and the levels of 14C in urine and tissues.

Ethylene oxide has been identified as a metabolite of ethylene in rodents based on its ability to form DNA and protein adducts (e.g. haemoglobin). The degree of alkylation obtained per unit exposure of ethylene oxide and ethylene shows that at low levels of ethylene, about 5-10% of the inhaled ethylene was metabolised to ethylene oxide in experimental animals. The rate of ethylene oxidation followed saturation kinetics with increasing concentration. *In vitro* studies using rodent liver also demonstrate that ethylene can be metabolised to ethylene oxide. Inducers (PCBs) of the mixed-function oxidase system can stimulate the metabolism of ethylene and increase the levels of exhaled ethylene oxide. A urinary metabolite 5-(2-hydroxyethyl)cysteine, possibly formed from ethylene oxide, was identified in mice.

B.6.2 Acute toxicity, irritancy and skin sensitisation studies (IIA 5.2)

B.6.2.1 Acute oral toxicity (IIA 5.2.1)

No studies submitted (or data cited from the published literature).

B.6.2.2 Acute dermal toxicity (IIA 5.2.2)

No studies submitted (or data cited from the published literature).

B.6.2.3 Acute inhalation toxicity (IIA 5.2.3)

Male rats exposed to ethylene at concentrations of 11.5, 28.8 or 65.6 mg/l of air for 4 hours showed increased serum pyruvate and liver weight at all dose levels (no deaths reported). The LC50 in male F344 rats was greater than 12.518 mg/l for a five hour exposure. The lethal concentration of ethylene in air to mice was stated to be 950000 ppm (estimated to be approximately 1093 mg/l of air). No respiratory irritation has been reported in patients. Therefore, ethylene would not be classifiable via the inhalational route according to EC criteria.

(Flury, 1928; Gaeb *et al*, 1975/OECD: SIDS)

B.6.2.4 Skin irritancy (IIA 5.2.4)

No studies submitted (or data cited from the published literature) but according to the reference there is no evidence that ethylene gas is a skin irritant.

(OECD: SIDS)

B.6.2.5 Eye irritancy (IIA 5.2.5)

No studies submitted (or data cited from the published literature) but according to the reference there is no evidence that ethylene gas is an eye irritant.

(OECD: SIDS)

B.6.2.6 Skin sensitisation (IIA 5.2.6)

No studies submitted (or data cited from the published literature).

B.6.2.7 Summary of acute toxicity, irritancy and sensitisation studies

Based on the cited data, ethylene is not classifiable via the acute inhalation route according to EC criteria. There is insufficient data to classify ethylene via the acute oral and dermal routes, for skin and eye irritancy or for skin sensitisation using the normal EC criteria. However, based on industrial use and practice and its use as an anaesthetic, ethylene gas dose not appear to be classifiable as a skin or eye irritant or a skin sensitiser. It should be noted that liquefied or pressurized ethylene gas can cause frostbite damage (this may trigger part of Directive 2003/82/EC).

B.6.3 Short-term toxicity studies (IIA 5.3)

B.6.3.1 Oral administration to rats

No studies submitted (or data cited from the published literature).

B.6.3.2 Oral administration to mice

No studies submitted (or data cited from the published literature).

B.6.3.3 Oral administration to dogs

No studies submitted (or data cited from the published literature).

B.6.3.4 Administration by other routes

B.6.3.4.1 Inhalation exposure

a) 6-day exploratory study

A group of six male Sprague-Dawley albino rats were exposed to a continuous flow of 60% ethylene in oxygen for 6 days, i.e. 600,000 ppm equivalent to 690 mg/l (1968 publication). Effects were reported on several haematology parameters. There was a significant reduction in thrombocyte count (-19.3%) and leukocyte count (-48.2%) and a reduction was also seen in the bone marrow cellularity (-30%).

(Fink, 1968/OECD: SIDS)

b) Liver damage occurred in mice repeatedly exposed (up to 20 times over 58 days) to atmospheric concentrations of 90% ethylene for periods of 60-90 minutes. There was no cellular injury in the kidney, adrenal, heart or lungs.

(Reynolds, 1926/BIBRA Toxicity Profile 1993)

c) 70-day study

Rats were exposed to ethylene at a concentration of 100 ppm (0.15 mg/l) for 70 days (non-GLP study reported in 1966 of unknown quality and no further exposure details). Changes in the reflex nerve impulses, a decrease in cholinesterase activity and reduced blood pressure were reported (no actual data or indications of the magnitude of these changes were reported).

(Krasovitskaya *et al*, 1966/ OECD: SIDS)

d) 90-day study

Groups of rats (15/sex/concentration) were exposed to ethylene at concentrations of 0, 300, 1000, 3000 or 10000 ppm (0, 345, 1150, 3450, or 11500 mg/$m^{3.}$ respectively) for 6 hours/day, 5 days/week for 13 weeks (a non-GLP study).

There were no differences between controls and treated rats with respect to total body weights, weight change, food consumption, haematology, clinical chemistry, gross pathology or histopathology. Male rats in the 0 (control), 300 and 10000 ppm groups showed red deposits or red discharge around the nose whereas the males in the 1000 ppm group had red deposits around the eyes. Amongst the female rats, a red deposit was discovered around the left eye of one 300 ppm female and alopecia around both ears of one 1000 ppm female. Compared with the controls, the liver weights in several groups of exposed rats were significantly lower (no indication of magnitude in the publication). There was no dose response relationship for this weight reduction and the cause was unknown. Ethylene appeared to have a low toxicity in rats when administered up to 10000 ppm (11.5 mg/l of air). This was considered to be the NOAEL for the 90-day study by the authors.

(Chemical Industry Institute of Toxicology, 1977/OECD: SIDS)

B.6.3.4.2 Dermal exposure

No studies submitted (or data cited from the published literature).

B.6.3.5 Summary of short term toxicity

No data were submitted for the oral or dermal routes of exposure (or cited from the published literature). A summary of the short-term inhalation data is presented in Table B.6.1.

The 6-day exploratory inhalation study in rats showed that at high exposure levels there were marked effects on the thrombocyte and leukocyte counts and on bone marrow cellularity. There are some limited citations that indicated the liver may be a target for ethylene induced toxicity. In the 70-day rat study, changes in the reflex nerve impulses, a decrease in cholinesterase activity and reduced blood pressure were reported. The 90-day inhalation study concluded that the NOAEL was greater than 11.5 mg/l of air for inhalation exposure, the highest dose tested. It should be noted that this study may have been conducted by Industrial Bio-Test Laboratories Inc under contract to the CIIT (see B.6.5). The background to IBT can be found at section 3.1.8 of http://www.oecd.org/dataoecd/13/15/36045203.pdf]

Table B.6.1 Summary of the short-term inhalation toxicity of ethylene

Type of study	NOAELs	LOEL/effects	Reference
6 day exploratory study in rats	Not set	600000 ppm (690 mg/l, the only dose tested): Marked effects on haematological parameters and bone marrow.	Fink, 1968/SIDS
70-day study in rats	Not set	100 ppm (0.15 mg/l): Changes in the reflex nerve impulses, a decrease in cholinesterase activity and reduced blood pressure.	Krasovitskaya *et al*, 1966/SIDS
90-day study in rats	11.5 mg/l	No effects reported at highest dose tested.	CIIT, 1977/SIDS

B.6.4 Genotoxicity studies (IIA 5.4)

B.6.4.1 *In vitro* testing (AII 5.4.1)

a) Bacterial mutations

Ethylene has been tested in an Ames test at atmospheric concentrations up to 20% in one strain (TA 100) of *Salmonella typhimurium* in the presence and absence of metabolic activation (non-GLP study/Victorin and Stalberg, 1988). It was also reported that previous testing in four strains of *Salmonella typhimurium* (non-GLP studies/Hamm *et al*, 1984; Hughes *et al*, 1984) and *in Escherichia coli* (non-GLP study/Landry and Fuerst, 1968) were also negative.

(OECD: SIDS)

b) Mutations in mammalian cells

No studies submitted (or data cited from the published literature).

c) Chromosome aberrations in mammalian cells

Duplicate cultures of Chinese hamster ovarian (CHO) cells were tested in the absence and presence metabolic activation (S9-mix) from Aroclor 1254-induced rats (GLP compliant study conducted to OECD guideline 473). The cells were tested at concentrations up to 280.5 mg/l (approximately 25% ethylene). Due to the explosive properties of ethylene when mixed with air, nitrogen was used as a carrier gas. The cells were exposed to a short 3 hour pulse treatment followed by a 17 hour expression period prior to harvest. Negative (carrier gas, untreated and positive control groups were tested. The positive control groups produced appropriate results. It was concluded that there was no effects on the mitotic index and no increase in the frequency of cells with structural chromosome aberrations.

(Riley, 1996/ OECD: SIDS)

B.6.4.2 *In vivo* genotoxicity in somatic cells (AII 5.4.2)

a) Micronucleus tests

Rats (10/dose) and mice (10/dose) were exposed to concentrations of 0, 40, 1000 or 3000 ppm for 6 hour/day, 5 days a week for 4 weeks (reported in 1994 but not stated whether or not GLP status). Bone marrow samples were collected approximately 24 hours after the final exposure. No significant differences in the PCE to NCE ratios

were observed in any exposure group. It was concluded that ethylene did not induce statistically significant concentration-related increases in the frequencies of micronucleated polychromatic erythrocytes in the bone marrow of rats or mice.

(Vergenes and Pritts, 1994/ OECD: SIDS)

b) Formation of DNA and haemoglobin adducts

Absorption, distribution, elimination of ethylene and formation of haemoglobin and DNA adducts were studied in rats after inhalation of 300 ppm ethylene for 12 hours per day for 3 consecutive days (a non-GLP study reported in 1995). DNA adduct formation was measured in liver and lymphocytes and haemoglobin adducts determined in erythrocytes. The adduct formation with ethylene was compared to other alkenes and adduct formation decreased with increasing number of carbon atoms in the molecule. No actual results or conclusions were provided in the publication (the study was stated to be an explorative study).

(Eide *et al*, 1995/OECD: SIDS)

c) Alkylation of DNA

Alkylation of 7-guanine was measured in DNA from liver spleen and testis of mice 14 hours after exposure by inhalation of 14C-ethylene at an initial concentration of 11 ppm for 8 hours (a non-GLP study reported in 1983). The degree of alkylation was much higher in the liver than in the other tissues. No actual results or conclusions were provided in the publication (the study was stated to be an explorative study).

(Segerback, 1983/OECD: SIDS)

B.6.4.3 *In vivo* studies in germ cells (AII 5.4.3)

No study submitted (or data cited from the published literature) but there are no indications in the available data/information that such a study is necessary.

B.6.4.4 Summary of genotoxicity studies

A summary of the submitted genotoxicity data is provided in Table B.6.2.

The bacterial mutation and chromosome aberration assays conducted with ethylene gas were stated to be negative for genotoxic activity (these conclusions may be equivocal taking into consideration the low solubility of ethylene in aqueous media). However, following *in vivo* inhalation exposure to rats and mice, the bone marrow micronucleus investigations were also reported to be negative (no significant differences in the PCE to NCE ratios). There was insufficient information provided for the DNA and haemoglobin adduct assays to draw any clear conclusions about the potential genotoxicity of ethylene.

The overall genotoxicity database on ethylene is limited, but on the data available there is no evidence for significant genotoxic potential.

Table B.6.2 Summary of the genotoxicity data

Study	Concentrations	Result	Reference
In vitro assays			
Ames test	Atmospheric concentrations up to 20%	Negative	OECD: SIDS
Chromosome aberrations in CHO cells	280.5 mg/l (approximately 25% ethylene)	Negative	Riley, 1996/ OECD: SIDS
In vivo assays (inhalation exposure)			
Bone marrow micronucleus tests in rats and mice.	3000 ppm (approximately 3.45 mg/l)	Negative	Vergenes & Pritts, 1994 OECD: SIDS
Formation of DNA and haemoglobin adducts	300 ppm (approximately 0.345 mg/l)	Adduct formation reported but no quantitative results reported	Eide *et al*, 1995 OECD: SIDS
Alkylation of DNA	11 ppm (approximately 0.0126 mg/l)	Alkylation reported but no quantitative results reported	Segerback, 1983 OECD: SIDS

B.6.5 Chronic toxicity and carcinogenicity studies (IIA 5.5)

A single long-term inhalation study has been summarised by the OECD: SIDS publication (CIIT, 1979/SIDS & by Hamm *et al*, 1984). However, this study was conducted 1977-1979 at the Industrial Bio-Test Laboratories Inc (IBT) under contract to the Chemical Industry Institute of Toxicology (CIIT). It should be noted that IBT was responsible for falsifying data which lead to the implementation of GLP principles and practice in the USA. The background to IBT can be found at section 3.1.8 of http://www.oecd.org/dataoecd/13/15/36045203.pdf]

B.6.5.1 Chronic dietary studies in rats

No studies submitted (or data cited from the published literature).

B.6.5.2 Chronic dietary study in mice

No studies submitted (or data cited from the published literature).

B.6.5.3 Carcinogenicity studies in rats

a) Fischer-344 inbred rats (120/sex/group) were exposed to ethylene at concentrations of 0, 300, 1000 and 3000 ppm for 6 hours per day, 5 day/week for up to 24months (non-GLP study).

The spontaneous mortality (15.7%) was stated to be roughly equal in all treated groups. Hair loss, deposits on and around the nose and eyes and gross eye abnormalities were noted but there were no obvious differences among the treatment groups. There was an overall increase in the number of animals exhibiting gross tissue masses for the test groups as compared with the control group but this trend was not statistically significant.

The final body weights and total weight changes for treated males were higher than those in the control groups but no dose related pattern was seen. There were no significant differences among any of the treatment groups on any of the haematology, blood chemistry or other parameters tested. No gross or histopathological tissue changes attributable to the effects of the test material were observed in any of the treated rats. The summary states that only a few findings were reported that could indicate any carcinogenic effect of the treatment.

In a publication from the above 1979 carcinogenicity study (Hamm *et al*, 1984), it was concluded that the results provided "no evidence that ethylene at these concentrations causes chronic toxicity or is oncogenic in Fischer 344 rats". However, this publication and the summary have been criticised since they do not discuss the mononuclear cell leukaemia described in the full report. It was stated that the number of animals affected (out of 90) rose from 12 and 8 in the male and female control groups to 21 and 11, respectively, in the groups receiving 3000 ppm. On the other hand, it has been stated that mononuclear cell leukaemia may occur in F344 rats at a background incidence > 75% and that a further increase in exposed animals is difficult to interpret with respect to human cancer development.

(Chemical Industry Institute of Toxicology/conducted by IBT, 1979/OECD: SIDS)

b) A summary of a 2-year rat inhalation study was submitted which was down loaded from the Hazardous Substances Data Bank (HSDB) on 5th May (toxnet.nlm.nih.gov). This summary appears to be another summary of the above 1979 inhalation study but provides some further limited information on the methodology. The maximum tolerated dose was not used as concentrations above 3000 ppm were considered hazardous because of the risks associated with the explosive properties of the test mixture. The calculated time weighted average concentrations for the 24 months of exposure were 0, 301, 1003 and 3003 ppm, respectively. Randomly selected animals were necropsied and examined after 6, 12 and 18 months and selected organs and tissues from all animals in the control and 3000 ppm groups were examined microscopically at termination. Histologically, a variety of proliferative, degenerative and inflammatory lesions were observed in both control and 3000 ppm groups. It was stated that these lesions were typical of those seen in this strain of animal and were unrelated to ethylene exposure.

(Hamm *et al*, 1984/HSDB)

c) Criticism of the above 2 year rat inhalation study and the Hamm summary has been published by BIBRA scientists.

"CIIT scientists concluded that there was 'no evidence that ethylene at these concentrations causes chronic toxicity or is oncogenic in Fischer 344 rats. According to the 'executive summary' of the full report (published separately), unusual malignant lung tumours were found in two rats exposed to 1000 ppm and one exposed to 3000 ppm, but the low incidence and lack of other related changes in bronchial epithelium suggested they may have occurred spontaneously. The incidence of mononuclear cell leukaemia is not discussed in the summary, but the full report (available only on microfiche) indicates that it was somewhat increased in both sexes at the top dose level. The number of animals affected (out of 90) rose from 12 and 8 in male and female controls to 21 and 11, respectively, at 3000 ppm. The total number of organs or

tissues affected rose to 106 in males and 83 in females from only 62 and 26, respectively, in controls. Whether it increased at lower doses too is uncertain, since only limited histological examination of the lower dose groups was conducted. In the view of EO to induce this form of cancer (NIOSH Current Intelligence Bulletin 1981, No5, 22 May) it is strange that the incidence of leukaemias is not discussed in the report's executive or by Hamm *et al,* 1984".

"Although one of the CIIT scientists was unable to detect any conversion of ethylene to EO in an *in vitro* preparation of rat-liver microsomes (Hamm *et al*. *loc. cit*.), two other metabolic studies indicate that rats and mice can indeed metabolize ethylene to EO and that both chemicals can lead to the alkylation of proteins and DNA."

(Rostron, 1986, Fd Chem Toxic, Vol 24 No 1)

d) Based on the pharmacokinetics of ethylene and its oxide in the rat, Bolt and Filser, 1987 estimated that exposure at an atmospheric concentration of 1000 ppm ethylene would correspond to a theoretical atmospheric concentration of 5.6 ppm ethylene oxide. Because of saturation kinetics, exposure concentrations of ethylene above 1000 ppm would not result in further increases in systemic ethylene oxide concentration. Thus, the above ethylene bioassay could not expose rats to more than 5.6 ppm ethylene oxide. By extrapolating the tumour/exposure data in the ethylene oxide studies to 5.6 ppm, the investigators concluded that the high ethylene exposures would not result in a tumour incidence of more than 2% above the background incidence. This lead to the conclusion that should ethylene pose a carcinogenic threat to the rat by virtue of its conversion to the oxide, the group sizes normally used in cancer study would be insufficient to produce statistically significant increases tumour yield at attainable ethylene concentrations.

(Hopkins, 1993, Fd Chem Toxic, Vol 32 No 2)

e) Groups of male and female Sprague-Dawley rats, there to five days of age, were exposed by inhalation to 0 (5 males and 9 females) or 11500 mg/m^3 or 10000 ppm (2 males and 10 females) ethylene (purity unspecified) for 8 hours per day on five days per week for three weeks. One week later, the rats received oral administration of 10 mg/bw Clophen A50 (a mixture of PCBs not otherwise specified) by gavage twice a week for up to eight additional weeks (promotion) at which time the experiment was terminated and the livers examined for ATPase-deficient foci. The number of ATPase-deficient foci in the rats exposed to ethylene did not exceed the control values. In the same experiment, ethylene oxide, administered as a positive control, produced a significant increase in the incidence of ATPase- deficient foci in females.

(Denk *et al*, 1988/IARC 1994)

B.6.5.4 Summary of chronic toxicity/carcinogenicity

No long-term studies were submitted for the oral route of exposure (or data cited from the published literature).

There are several summaries in the published literature of a single long-term inhalation study in the rat. Generally, the authors of these summaries have concluded that there no evidence of chronic toxicity in this study and no evidence of compound-induced carcinogenicity. However, some authors have expressed doubts over the interpretation of the findings in this study (i.e. the mononuclear cell leukaemia). Although IARC

(1994) concluded that the evidence of carcinogenicity in experimental animals and humans was inadequate, Tornqvist (1994) and Hopkins (1993/OECD: SIDS) stated that the possible carcinogenic risk from inhaling ethylene should be reconsidered/re-evaluated based on the potential exposure to ethylene (very high tonnage), the limited database and the metabolism of ethylene to ethylene oxide.

B.6.6 Reproductive and developmental toxicity studies (IIA 5.6)

A multigeneration study has not been submitted instead a summary of a single generation screening test has been submitted to support the application. The limitations of such a protocol for the detection of compound-induced post-natal effects and the small number of animals tested should be noted.

B.6.6.1 Fertility and post-natal developmental toxicity

a) Reproduction/Development Toxicity Screening Test (IIA 5.6.1)

Rats (10/sex/concentration) were exposed to ethylene (head only) at concentrations of 0, 200 (230 mg/m^3), 1000 (1150 mg/m^3) or 5000 ppm (5750 mg/m^3) for 6 hours daily (the number of days/week was no stated). The calculated body burden was approximately 0, 80, 400 and 2000 mg/kg bw/day for the dosing regime. Since the uptake from the lungs is likely to be in the range of 5-10%, the actual absorbed dose would be substantially less than the values given above. This study was GLP compliant and carried out in accordance with OECD Guideline 421 (Reproduction/Development Toxicity Screening Test).

The test material was administered to parent animals for two weeks prior to mating, during the mating period and until the day prior to necropsy for the males (minimum 28 days) and until day 20 of gestation for the females. The females were allowed to litter and rear their offspring to day 4, post-partum, when they and their offspring were killed.

Morbidity, mortality, clinical condition, weights and food intake were observed throughout the study, and mating was carefully observed. For each female, litter data and also observations for each offspring were recorded. At termination of the study, all animals were subject to macroscopic examination for structural or pathological changes. Ovaries, testes and epididymides of the control and high dose animals were subject to a histopathological examination.

There were no deaths attributable to the test article, and body weight gain was not adversely affected during the pre-pairing, gestation or lactation periods. The treatment had no effect on fertility or fecundity and all females became pregnant. Litter size, sex ratio, mean pup weight and pup growth and clinical condition were not adversely affected by treatment.

Necropsy revealed no macroscopic finding suggestive of toxicity due to test article administration. There was no evidence of any toxic effect on the testis due to test substance administration and there were no other microscopic findings suggestive of toxicity due to test article administration.

The summary concluded that at nominal concentrations of 200, 1000 or 5000 ppm there was no evidence of toxicity or adverse effects on male and female reproductive performance, fertility, pregnancy, maternal and suckling behaviour and growth and development of the offspring from conception to Day 4, post-partum. The NOEL was established to be 5000 ppm (equivalent to 5.75 mg/l) with respect to parental toxicity and foetal and reproductive performance.

(Aveyard, 1996/OECD: SIDS)

b) Post natal-development

In a published study, newborn rats exposed to a concentration of 2.62 ppm (approximately 0.003mg/l) for 90-days (continuous inhalation) exhibited a delay in coat appearance, dentition and eye opening; circulation hypotension, cholinesterase inhibition and subordination disruption were also reported. It was stated that there was no information on the quality of this study.

(Krasovitskaya and Mabyarova LK, 1968/OECD: SIDS)

B.6.6.2 Developmental toxicity studies (IIA 5.6.2)

a) Developmental study in rats

No studies submitted (or data cited from the published literature).

b) Developmental study in rabbits

No studies submitted (or data cited from the published literature).

B.6.6.3 Summary of reproductive toxicity

The reproductive screen test concluded there was no compound induced parental or foetal toxicity or developmental toxicity over a single generation (i.e. up to 4 days post partum) at concentrations up to 5.75 mg/l (equivalent to a systemic exposure of 0.575 mg/l). However, some published data (of unknown quality) appears to indicate that post-natal development could be adversely affected at low dose levels.

B.6.7 Neurotoxicity studies (IIA 5.7)

B.6.7.1 Delayed neurotoxicity studies

Ethylene is not of similar or related structure to those compounds such as the organophosphates that are capable of inducing delayed neurotoxicity. Therefore, delayed neurotoxicity studies have not been carried out.

B.6.7.2 Acute and repeat dose neurotoxicity studies

No studies submitted (or data cited from the published literature).

B.6.7.3 Summary of the neurotoxicity studies

No specific neurotoxicity studies have been submitted for evaluation but there are some indications of treatment-related effects on the nervous system. Two papers by the same authors have reported changes in the reflex nerve impulses, a decrease in cholinesterase activity and reduced blood pressure. Although there is no information on the quality of the investigations or the magnitude of the changes in these two papers, it should be noted that nerve impulses, cholinesterase activity and blood pressure have not been routinely investigated in the standard toxicity studies.

B.6.8 Further toxicological studies (IIA 5.8)

B.6.8.1 Relevant metabolites (ethylene oxide)

Since ethylene is metabolised to ethylene oxide in experimental animals and humans, a summary of the submitted published data/information for ethylene oxide has been included in this evaluation. It should be noted that the majority of data for ethylene oxide has been primarily generated using the inhalation exposure route.

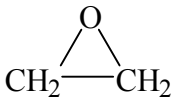
Ethylene oxide is officially classified by the ECB as a Cat: 2 for carcinogenicity (R45) and Cat: 2 for mutagenicity (R46). In addition, the literature indicates that ethylene oxide induces reproductive effects in experimental animals (foetal toxicity in the presence and absence of maternal toxicity, teratogenicity in mice, sperm effects) and there is some limited evidence of spontaneous abortions in humans.

Ethylene oxide is also officially classified by the ECB as Toxic by inhalation (R23) and as an irritant (R36/37/38). The literature also indicates that it can also induce sensitisation responses.

An updated MSDS (2005) obtained from the internet suggests that ethylene oxide may be classifiable for acute oral and dermal toxicity (R24 & 25); an acute oral LD50 value of 72 mg/kg bw is cited by this MSDS.

The current UK cut-off for ethylene oxide in pesticide formulations is the limited of detection (LOD) and the occupational maximum exposure level is 5 ppm; 8-hour TWA (EH64 Summary Criteria for Occupational Exposure Levels, as amended by update supplements up to 2002).

Figure B.6.2 Structure of ethylene of ethylene oxide



ethylene oxide

Chemical name: ethylene oxide.
CAS Number: 75-21-8.
Other names: dihydrooxirene, dimethylene oxide, EO, ETO, 1,2-epoxyethane, epoxyethane, ethene oxide, oxacyclopropane, oxane, oxidoethane and oxirane.
Molecular weight: 44.05 g/mol.
Octanol/water partition coefficient: Log Kow = -0.30.
Solubility in water: infinitely soluble.
Vapour pressure: 146 kPa @ 20 ºC
Physical state: Colourless gas at normal temperature and pressure.
Smell: described as having a characteristic ethereal odour.
Odour threshold: 470 mg/m^3 for perception and 900-1260 mg/m^3 for recognition.
Conversion factors (NTP): i) 1 ppm = 1.8 mg/m^3; at 25ºC, ii) 0.55 ppm = 1.0 mg/m^3.
Methods of production: i) catalytic oxidation of ethylene with air or oxygen, ii) the chlorohydrin process.

Ethylene oxide is an important industrial chemical. It is used as an intermediate in the production of various chemicals (e.g. ethylene glycol & surfactants), as a sterilant, a fumigant and as a component of pest control products. Gas and liquid forms of ethylene oxide may be released into the environment during industrial processes and sterilisation operations (e.g. medical equipment in hospitals). It is also released on combustion of fossil fuels and is present in tobacco smoke.

Ethylene (a natural plant growth regulator) is degraded to ethylene oxide in certain plants and by certain micro-organisms. Ethylene oxide is also produced by some natural sources such as manure and sludge.

Ethylene oxide is used as a sterilant (micro-organisms) and fumigant (insects) on food stuffs at concentrations that range from 250-1500 mg/litre (ECHC 2001).

The data/information in this section has mainly been taken from the following publications:

i) International Programme on Chemical Safety (IPCS). World Health Organisation (WHO). 1985 Environmental Health Criteria 55. Ethylene Oxide (WHO 1985).

ii) Environment Canada & Health Canada. Priority Substances List Assessment Report (September 2001): Ethylene oxide (ECHC 2001).

iii) IARC Monograph on the Evaluation of Carcinogenic Risks to Humans (1994). Some Industrial chemicals, Vol 60 (Ethylene oxide, pages 73-159) (IARC 1994).

iv) IPCS. WHO. Concise International Chemical Assessment Document 54 (2003) (CICADS 2003).

Inevitably, the publications listed above are mainly summarising and citing the same data and studies. Since there are minor differences in the reporting of the details by the different sources, individual studies may be cited more than once especially where additional information has been reported.

B.6.8.1.1 Absorption, distribution, excretion and metabolism

Absorption, distribution and excretion

a) Inhalation studies in mice show that ethylene oxide is very soluble in blood and the pulmonary uptake is expected to be rapid and to depend only on the alveolar ventilation rate and the concentration of ethylene oxide in the inspired air. The rate of uptake of ethylene oxide was 1.1µg/kg bw per min at an exposure level of 1 mg/m^3. This corresponds to nearly 100% absorption of ethylene oxide from 1.1 litre of air per min and per kg bw which is the reported rate of alveolar ventilation in resting mice. Approximately 74% of labelled ethylene oxide inhaled by mice was excreted in the urine within 24 hours in the form of unidentified metabolites.

(Ehrenberg *et al*, 1974/WHO, 1985)

b) Ethylene oxide is rapidly distributed throughout the body. In mice, whole body autoradiograms 2 min after intravenous injection showed that concentrations of ethylene oxide in the liver, kidneys, and pancreas were 3-4 times those in the blood. Between 20 minutes and 4 hours after exposure, radioactivity was distributed throughout the body. Directly after inhalation by mice, the highest concentrations of labelled ethylene oxide were found in the liver, kidney, and lung. The radioactivity in the liver and kidney dropped exponentially and approached the levels in the lung, testes, spleen, and brain within 4 hours, indicating rapid metabolism and excretion (Appelgren *et al*, 1977). On the basis of tissue alkylation data (Ehrenberg *et al*, 1976) or haemoglobin alkylation data (Osterman-Golkar *et al*, 1976), a half-life of approximately 10 min was estimated for the first-order clearance of ethylene oxide from mouse or rat tissues. A similar value for man was estimated on the basis of haemoglobin alkylation data (Calleman *et al*, 1978).

(WHO, 1985)

c) When the degree of protein and DNA alkylation was investigated in mice and rats, only small variations were observed between the different tissues in the species. Apparently, most organs receive a more or less equal dose of ethylene oxide after distribution throughout the body. The extent of protein alkylation was approximately equal in the lung, liver, kidney, and spleen of mice, 120 min after inhalation of 2 mg ethylene oxide/m^3 air, for 75 min, but in the testes, it was about 50% lower. When the vapour concentration was increased (up to 59 mg/m^3), the degree of protein alkylation in the liver increased relative to that in the other tissues. In all the tissues investigated, protein alkylation increased linearly with the dose up to an exposure level of 59 mg/m^3 and was relatively constant for at least 3.5 hours following exposure.

(Ehrenberg *et al*, 1974/WHO, 1985)

d) When 0.4 mg ethylene oxide/kg body weight was administered intraperitoneally to mice, DNA alkylation in the testes and spleen was, respectively, 50 and 40% of that in the liver, 5 hours after exposure. The approximate half-lives of the alkylation products were 24 hours in the spleen, 10 hours in the testes, and 12 hours in the liver. For the spleen, this half-life was found to be shorter *in vivo* than *in vitro,* indicating active removal.

(Segerback, 1983/WHO, 1985)

Metabolism

The available animal data indicate two possible pathways for the metabolism of ethylene oxide, i.e., hydrolysis to 1,2-ethanediol and conjugation with glutathione (Fig. B.6.2).

a) In dogs, peak levels of 13 and 33 mg 1,2-ethanediol/litre blood-plasma were measured between 1 and 3 hr after intravenous administration of 25 or 75 mg ethylene oxide in water/kg body weight, respectively. As the half-life for hydrolysis is about 60 h at 40 °C in neutral fresh water, the involvement of an epoxide hydrolase has been suggested, but this has not yet been confirmed. The peak concentration of 1,2-ethanediol at 25 mg ethylene oxide/kg body weight represented approximately 25% of the dose of ethylene oxide. Within 24 hr, 7-24% of the dose was excreted in the urine as 1,2-ethanediol.

(Martis *et al*, 1982/WHO, 1985)

b) In the serum of workers exposed to ethylene oxide (0.54-27 m^3 air; mean 7.56 m^3 air,), for an average of 5.3 years, the blood concentration of 1,2-ethanediol was elevated compared with that of unexposed controls.

(Wolfs *et al*, 1983/WHO, 1985)

c) The results of studies in rats, rabbits and monkeys have shown that some 1,2-ethanediol is metabolised but most of it is excreted unchanged in urine.

(Gessner *et al*, 1961; McChessney *et al*, 1971/WHO, 1985)

d) When a single dose of 2 mg labelled ethylene oxide in propanediol was administered intravenously to rats 43% was excreted in urine within 50 hours (41% within 24 hours); 9% as S-(2-hydroxyethyl)cysteine and 33% as N-acetyl- S-(2-hydroxyethyl)cysteine. Ethylene oxide (1%) and labelled carbon dioxide (1.5%) were also excreted via the lungs.

(Jones and Wells, 1981/WHO, 1985)

e) As ethylene oxide can react with chloride ions, and this reaction is acid catalysed, 2-chloroethanol might be expected to be a metabolite, especially after oral administration. However, neither 2-chloroethanol (also called ethylene or glycol chlorohydrin), nor its metabolites have been found in the plasma, tissues, or urine of species exposed to ethylene oxide.

(Grunow & Altman, 1982/WHO, 1985)

B.6.8.1.2 Dermal penetration

a) *In vitro*

The permeation rate of a solution of 1% ethylene oxide in water (w/v) through excised human skin at 30ºC was determined to be 0.125 mg/cm^2/hour.

(Baumbach *et al*, 1987/IARC 1994)

b) *In vivo*

The range of skin penetration of ethylene oxide was reported to be 1-14% from a variety of formulated products.

(Kreuzer, 1992/ECHC 2001)

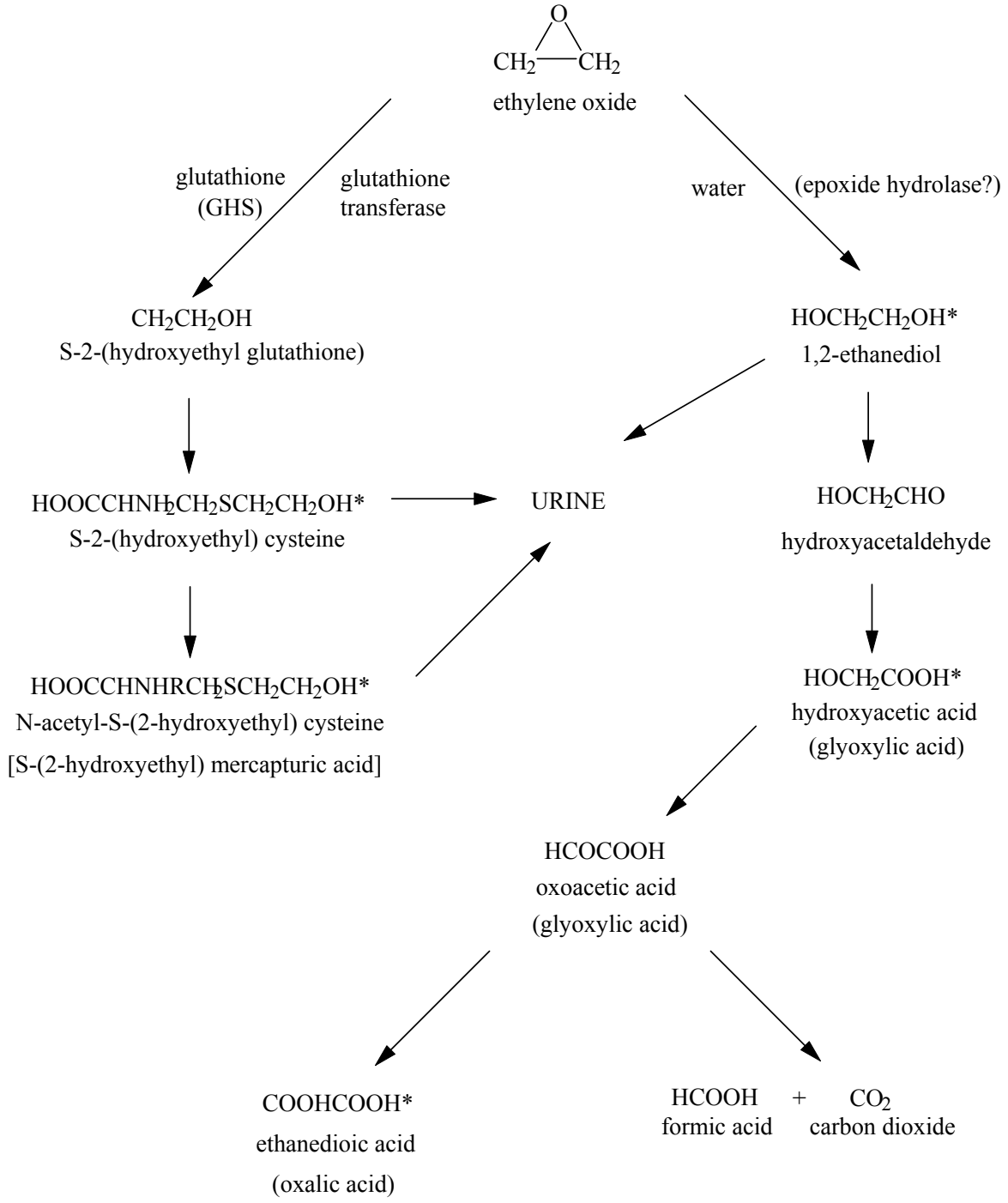
B.6.8.1.3 Summary of ADME studies

No ADME studies using oral administration of ethylene oxide have been submitted (or cited from the literature).

Inhalation and intravenous administration of labelled ethylene indicate that the excretion occurs mainly via urine. Minor amounts of unchanged parent and labelled carbon dioxide are excreted via the lungs. Distribution is widespread based on the protein and DNA alkylation in various organs and tissues (e.g. lung, liver, kidney, spleen and testes).

Two metabolic pathways have been identified in experimental animals and humans, the hydrolysis of ethylene oxide to 1,2-ethanediol and conjugation with glutathione to produce S-(2-hydroxyethyl)cysteine and N-acetyl- S-(2-hydroxyethyl)cysteine.

Figure B.6.3 Proposed pathway for the metabolism of ethylene oxide in mammals



KEY: a) * metabolites identified by Gessnar et al, 1961; McChessney et al, 1971; Jones and Wells, 1981. b) GSH = glutamylcysteinylglycine. c) R = $COCH_3$ d) Taken from WHO, IPCS, Environmental Health Criteria 55, Ethylene Oxide.

B.6.8.1.2 Acute toxicity, irritancy and sensitisation

B.6.8.1.2.1 Acute oral toxicity

a) The acute LD50 values cited for ethylene oxide administered orally (in water) to rodents were 330 mg/kg bw for male rats and 365 and 280 mg/kg bw for male and female mice, respectively.

(Smyth *et al*, 1941; Woodward & Woodward 1971/WHO 1985)

b) A MSDS (updated 2005) reports an acute LD50 value of 72 mg/kg bw for ethylene oxide in the rat.

(http://www.physchem.ox.ac.uk/MSDS/ET/ethylene_oxide.html)

c) After oral administration to rats, the difference between 0.1% mortality (325 mg/kg) and 99.9% mortality (975 mg/kg) was approximately 650 mg/kg body weight.

(Smyth *et al*, 1941/WHO, 1985)

B.6.8.1.2.2 Acute dermal toxicity

A MSDS (updated 2005) states that ethylene oxide is classified as 'Toxic in contact with skin'.

(http://www.physchem.ox.ac.uk/MSDS/ET/ethylene_oxide.html)

B.6.8.1.2.3 Acute inhalation toxicity

a) Ethylene oxide was stated to be toxic by inhalation with 4 hour LC50 values of 1460, 835 and 960 ppm (2672, 1528 and 1757 mg/m^3) for rats, mice and dogs, respectively. No deaths occurred in dogs at 1280 mg/m^3. No guinea pigs died after inhalation of ethylene oxide at a level of 450 mg /m^3 air for 8 hours, the majority died at 2400 mg/m^3. Guinea pigs exposed to ethylene oxide at a concentration of 13000 mg/m^3 for 2.5 hours were found lying on their sides and unable to stand.

In the above studies, the respiratory system and nervous system were the main targets in rodents and dogs. The clinical effects included nasal irritation, scratching the nose, nasal discharge, lachrymation, salivation, respiratory effects (gasping and laboured breathing) vomiting and convulsions. The gross findings in animals that died included congestion and oedema in the lungs, petecchial haemorrhage of the trachea and hyperaemia of the liver and kidneys and parenchymatous changes in the kidneys.

(Jacobson *et al*, 1956; Waite *et al*, 1930/WHO, 1985)

b) A MSDS (updated 2005) states the LC50 for ethylene oxide in the rat for a 4 hour exposure was 800 ppm (920 mg/m^3).

(http://www.physchem.ox.ac.uk/MSDS/ET/ethylene_oxide.html)

c) Male and female mice were exposed to concentrations of up to 1600 ppm (2928 mg/m^3) for 4 hours. At 800 ppm (1464 mg/m^3), all the males and 4 of the 5 females died within six days post exposure.

(Jacobson *et al*, 1956/WHO, 1985)

B.6.8.1.2.4 Skin irritancy

a) Cotton pads moistened with solutions of 100 or 500 g ethylene oxide/litre water were applied to shaved rabbit skin under a plastic cover. After an exposure period of six minutes, skin irritation (with hyperaemia), oedema and scar formation were observed. The intensity of the response was reported to be roughly proportional to the length of exposure time (1 - 60 min) and the concentration.

(Hollingsworth *et al*, 1956/WHO, 1985)

B.6.8.1.2.5 Eye irritancy

a) A maximal non-damaging concentration of 0.1% ethylene oxide in physiological salt solution was established after instillation of 0.05 ml solution, every 10 minutes for 6 hours, into the conjunctival sac of rabbits. The concentration above 1% caused reversible changes in conjunctiva such as hyperanemia and swelling and irreversible opacity both in the cornea and in the lens. *In–vitro* studies with isolated rabbit cornea were in agreement with these results.

(McDonald *et al*, 1973; Edelhauser *et al*, 1983/WHO, 1985)

B.6.8.1.2.6 Skin sensitisation

a) No study submitted (or data cited from the published literature).

b) Ethylene oxide is considered a strong sensitising agent owing to its strong reactivity with various chemical groups (anaphylaxis and contact dermatitis are reported in humans).

(Bommer and Ritz, 1987/ECHC 2001)

B.6.8.1.2.7 Summary of acute toxicity, irritancy and sensitisation

A summary of the cited acute toxicity data is presented in Table B.6.3.

A steep dose response curve was evident for ethylene oxide from the reported mortalities in the acute studies. These studies indicate that the respiratory system, the nervous system and the liver and kidneys are target organs. It should also be noted that liquefied or pressurized ethylene oxide gas can cause frostbite damage (Hine & Rowe, 1981/).

The official ECB classification of ethylene oxide: Cat 2: carcinogenicity, Cat: 2 mutagenicity, Toxic by inhalation (R23) and R/36/37/38 for irritancy.

Table B.6.3 Summary of the acute toxicity, irritancy and skin sensitisation of ethylene oxide

Study	Species	Results/comments	Classification	Reference
Acute oral	Rat	72 mg/kg bw.	Toxic (R25)	physchem.ox.ac.uk
Acute oral	Rat	Males: 330 mg/kg bw	Harmful (R22)	WHO, 1985
Acute oral	Mouse	♂ & ♀: 365 & 280 mg/kg bw, respectively.	Harmful (R22)	
Acute dermal	NS	No details given	Toxic (R24)	physchem.ox.ac.uk
Acute inhalation	Rat	2.672 mg/l	Harmful (R20 & R37)	WHO, 1985
Acute inhalation	Rat	0.92 mg/l	Toxic (R20 & R37)	physchem.ox.ac.uk
Acute inhalation	Mouse	1.528 mg/l	Toxic (R23 & R37)	WHO, 1985
Acute inhalation	Dog	1.757 mg/l	Toxic (R23 & R37)	WHO, 1985
Skin irritation	Rabbit	Aqueous solutions	Irritating to skin (R38)	WHO. 1985
Skin sensitisation	NA	Considered to be a sensitiser based on chemical reactivity.		

Key: a) NS = not stated in MSDS/citation. b) NA = not applicable.

B.6.8.1.3 Short-term toxicity

The cited data for short-term repeat dose toxicity is primarily limited to inhalation studies.

B.6.8.1.3.1 Oral administration to rats

In a reported subacute study, rats orally exposed to ethylene oxide at 100 mg/kg bw/day in olive oil for 5 days/week for 3 weeks (15 doses in 21 days). The findings included loss of body weight, gastric irritation and slight liver damage.

(Hollingsworth *et al*, 1956/WHO 1985)

B.6.8.1.3.2 Oral administration to mice

No studies submitted (or data cited from the published literature).

B.6.8.1.3.3 Oral administration to dogs

No studies submitted (or data cited from the published literature).

B.6.8.1.3.4 Inhalation exposure data/information for experimental animals

a) Groups of Wistar rats (10-20/sex), guinea pigs (8/sex), rabbits (1-2/sex) and Rhesus monkeys (1-2 females) were each exposed to concentrations of ethylene oxide at levels of 0, 90, 200, 370, 640, or 1510 mg/m^3, for 7 hours per day/5 day per week. The female monkeys were not tested at 90 mg/m^3 and an additional 3 male monkeys were tested at 640 mg/m^3. The test period varied with the species tested and the severity of exposure, i.e. approximately 26 weeks at 90 mg/m^3; 25-32 weeks at 200 and 370 mg/m^3; 7-25 weeks at 640 mg/m^3 and 10 days at 1510 mg/m^3.

Guinea pigs, rabbits, and monkeys tolerated 90 and 200 mg/m^3 and rats tolerated exposure to 90 mg/m^3 without adverse effects on general appearance, behaviour, mortality rate, growth, body and organ weight and gross and microscopic examination. Rats showed elevated mortality rates from 370 mg/m^3, rabbits from 640 mg/m^3 and all exposed animals died at 1510 mg/m^3. Secondary respiratory infection was put forward as a cause of death in an appreciable number of rats and mice in these studies.

Surviving rats showed increased relative lung weights after 26-27 weeks at 200 and 370 mg/m^3. At 370 mg/m^3, haemorrhages, hyperaemia, emphysema, and local alveolar collapse were observed in these lungs. Lungs of male rabbits also showed hyperaemia and slight oedema at 370 mg/m^3. Even more severe lung injury was seen in rats at 640 mg/m^3 and the higher exposure. Gross respiratory tract irritation was apparent in all species at 1510 mg/m^3.

Delayed reversible effects were observed on the peripheral nervous system. Monkeys and rabbits exhibited paralysis of the hind legs at 370 mg/m^3 and rats at 640 mg/m^3. This was accompanied by atrophy of the muscles of the hind legs (except in rabbits at 370 mg/m^3). The effects on the peripheral nervous system were investigated further in monkeys and loss of both sensory and motor function was noted at levels of 370 and 640 mg/m^3.

Significant increases in body weight were also observed in rats, at levels of 200 mg/m^3 or more. Rats showed slight but significant increases in the relative weights of kidney and liver at 370 mg/m^3.

(Hollingworth *et al*, 1956/WHO, 1985)

b) Groups of 20 male rats and 30 female mice were exposed to concentrations of ethylene oxide at levels of 0, 180, or 730 mg/m^3 for 6 hours/day/5 days per week. The exposures lasted 26 weeks at 180 mg/m^3 and 6 weeks at 730 mg/m^3. Additional groups of 15 rats and mice at the higher and 60 rats and mice at the lower exposure level were used for interim gross pathology.

No clear toxic effects were reported at 180 mg/m^3. No pathological changes were observed except for marked haemosiderosis in the spleen of a few rats at 730 mg/m^3. The highest exposure (730 mg/m^3) resulted in death for both species without clinical signs in mice. Effects on the respiratory and nervous system were shown by rats as laboured breathing, reddish nasal discharge, diarrhoea, tendency towards a side position, and dragging of the hind-quarters. Rats also lost weight, which was regained by survivors.

(Jacobson *et al*, 1956/WHO, 1985)

c) Groups of 30 B6C3F1 mice of each sex were exposed to concentrations of ethylene oxide at 0, 18, 86, 187, or 425 mg/m^3, for 6 hr/day, and 5 days per week. The exposures lasted for 10 weeks for males and 11 weeks for females. No effects were observed in relation to survival, body weight, clinical signs, white blood cell count, serum clinical chemistry, urinalysis and histopathology. At the highest exposure level, changes at terminal sacrifice included an increased relative liver weight in female mice, and a decreased testicular weight in males. A decreased relative spleen weight was observed at 187 and 425 mg/m^3 in both sexes. In addition, the red blood cell

count, the packed cell volume, and the haemoglobin concentrations were decreased at 425 mg/m^3. Screening of neuromuscular function at week 6 (5 female mice) and weeks 10 or 11 (5 mice/sex) revealed altered reflex responses at 425 mg/m^3 and a dose-related trend in alterations of locomotor function from 86 mg/m^3 upwards.

(Snellings *et al*, 1984a/WHO, 1985)

d) Groups of 3 male beagle dogs each were exposed to concentrations of ethylene oxide of 180 and 530 mg/m^3, for 1-3 days. No effects were observed on mortality rate, body weight, electrocardiogram, blood-calcium and -urea, icteric index and rectal temperature. Anaemia was noted at both exposure levels. Effects on the respiratory and nervous systems were shown at 530 mg/m^3, such as hyperaemia and local alveolar collapse in lungs, vomiting, and occasional slight tremors and transient weakness in the hind legs. Muscular atrophy was also observed.

(Jacobson *et al*, 1956/WHO, 1985)

e) New Zealand rabbits (3 males/dose) were exposed to 0, 18, 90, or 450 mg/m^3.for 12 weeks. No haematological changes were noted.

(Yager & Benz, 1982/WHO, 1985)

f) Fischer rats (groups of 3 or 4 animals) were exposed to 90, 270, or 810 mg/m^3 for 6 hours per day for 3 days. The white blood cell count was depressed but there was a poor correlation with exposure level.

(Kligermann *et al*, 1983/WHO, 1985)

B.6.8.1.3.5 Dermal exposure

No studies submitted (see section B.6.8.1.2).

B.6.8.1.3.6 Summary of short term toxicity

A summary of published short-term toxicity data are presented in Table B.6.4.

Following oral exposure in a subacute study, loss of body weight, gastric irritation and slight liver damage were evident (no further details).

Following inhalation exposure, mortalities and effects on respiratory system, the haematological system (including bone marrow), the nervous system, ocular lens, liver and kidneys, thymus and spleen and the testes were reported. A dose-related in crease in pulmonary adenoma was also seen in mice after 6 mounts of exposure.

Table B.6.4 Subchronic effects of exposure to ethylene oxide, presented in tabulated form (taken from IARC 1994)

Species	Exposure	Effects
General toxicity		
Wistar rats (♂)	0 & 500 ppm (915 mg/m^3), 6 hours/day, 5 days/week for 13 weeks.	**500 ppm** i) Decrease in glutathione reductase in the brain, liver, ocular lens and erythrocytes (and glutathione). ii) Increase in lipid peroxidation in the liver (malondialdehyde liver). iii) Anaemia (normocytic and normochromic) decrease in the haemoglobin concentration. iv) Disturbance of porphyrin-haem metabolism. v) Decrease in hepatic cytochrome P450.
Wistar rats (♂ & ♀)	0 & 250 ppm (458 mg/m^3), 6 hours/day, 5 days/week for 17 weeks.	**250 ppm** i) Decrease in hepatic cytochrome P450 in males. ii) Decrease in hepatic glutathione reductase and an increase in glutathione-S-transferase (both sexes). iii) Increase in hepatic NADPH-cytochrome c reductase and liver weight in females. iv) Increase in hepatic glutathione peroxidase.
B6C3F1 mice (♂ & ♀)	0-250 ppm (0-458 mg/m^3), 6 hours/day, 5 days/week for 10 weeks (♂) or 11 weeks (♀).	**250 ppm** i) Decrease in spleen weight and an increase in liver weight in females. ii) Decrease in absolute testicular weight. iii) Slight decrease in haemoglobin concentration and erythrocyte count. **100 ppm (183 mg/m^3)** i) Decrease in spleen weight in females.
[a]B6C3F1 mice (♂ & ♀)	0-600 ppm (0-1098 mg/m^3), 6 hours/day, 5 days/week for 14 weeks.	**600 ppm (1098 mg/m^3)** i) Renal tubular necrosis. ii) Lymphocytic necrosis of the thymus and spleen in males. **200-600 ppm (366-1098 mg/m^3)** i) Rhinitis of the nasal cavity. **100-400 ppm (366-1098 mg/m^3)** i) Renal tubular degeneration. Also dose-related epithelial damage in the nasal portion of the respiratory tract.
C57BL/6J mice (♂)	0 & 255 ppm (467 mg/m^3), 6 hours/day, 5 days/week for 16 days; 6 hours/day, 5 days/week for 4-10 weeks.	**255 ppm** General depression of cellularity in blood and bone marrow (with large fluctuations) and transient increase in granulocytes.
ddY mice (♂)	0 & 400 ppm (732 mg/m^3), 6 hours/day, 3 days/week for 13 weeks.	**400 ppm** i) Macrocytic anaemia ii) Two-fold increase in hepatic cytochrome P450 iii) Increase in ferricyanide reductase. iv) Decrease in hepatic glutathione reductase and glutathione peroxidase. v) Increase in hepatic glutathione-S-transferase.

Key: a) US National Toxicology Program (1987).

Table B.6.4 Subchronic effects presented in tabulated form (taken from IARC)

Neurotoxicity		
Species	**Exposure**	**Effects**
Wistar rats (♂)	0 & 250 ppm (458 mg/m^3), 6 hours/day, 5 days/week for 9 months.	**250 ppm** i) Preferential distal axonal degeneration of myelinated fibres in sural nerves and gracile fascicles.
Wistar rats (♂ & ♀)	0 & 250 ppm (458 mg/m^3), 6 hours/day, 5 days/week for 17 weeks.	**250 ppm** i) Paresis of hindlegs ii) Degeneration of myelinated fibres in the peroneal nerve, the nerve of the soleus muscle and gracile fascicles. iii) No sex differences.
Wistar rats (♂)	0 & 500 ppm (915 mg/m^3), 6 hours/day, 3 days/week for 13 weeks.	**500 ppm** i) Ataxic gait after 6 weeks ii) Preferential distal axonal degeneration of myelinated fibres in hindleg nerves and gracile fascicles. iii) Decrease in creatine kinase activity in serum, brain and spinal cord after four weeks.
B6C3F1 mice (♂ & ♀)	0-250 ppm (0-458 mg/m^3), 6 hours/day, 5 days/week for 10 weeks (♂) or 11 weeks (♀).	**0-250 ppm** i) Dose-related trend in reduction in locomotor activity and abnormal reflexes. ii) No microscopic findings.

B.6.8.1.4 Genotoxicity

Ethylene oxide is an alkylating agent and is considered to be a mutagen in experimental animals and humans. It has consistently displayed genotoxic activity in almost all *in-vitro* and *in vivo* studies reviewed by the cited publications (see B.6.8.9 for human data/information).

(IARC 1994)

B.6.8.1.4.1 *In vitro* testing

Ethylene oxide is an alkylating agent. It has induced gene mutations in plant, bacteria, fungi, insect, mammalian and human cells (*in vitro* investigations with and without metabolic activation). Numerous studies in mammalian cells are reported in the literature showing gene mutations, micronucleus formation, chromosome aberrations, cell transformation, unscheduled DNA synthesis, DNA strand breaks and sister chromatid exchanges.

(WHO 1985 & IARC 1994)

B.6.8.1.4.2 *In vivo* genotoxicity in somatic cells

The available *in vivo* studies have reported positive results following administration by ingestion, inhalation or intraperitoneal injection of ethylene oxide. Genotoxic activity has been reported in rats, mice, rabbits and monkeys and includes the endpoints list below.

i) Formation of DNA adducts (haemoglobin used as a surrogate for DNA adducts) in brain, kidney, lung and spleen (rats and mice).

ii) Gene mutations in rat and mouse splenic T-lymphocytes (HPRT locus) and in the lung (lacI locus) of transgenic mice.

iii) Sister chromatid exchanges in lymphocytes (rabbits, rats and monkeys) and bone marrow cells (rats and mice).

iv) The induction of sister chromatid exchanges appears to be a more sensitive endpoint than chromosome aberrations and the formation of micronuclei.

v) Micronucleus formation in bone marrow cells (rats and mice).

vi) Chromosome aberrations in lymphocytes (monkey) and bone marrow cells (rats and mice).

(WHO 1985 & IARC 1994)

B.6.8.1.4.3 *In vivo* studies in germ cells

a) Ethylene oxide also induces heritable mutations or effects in germ cells. Dose-related damage to germ cells was established in the mid and late spermatid stages in a mouse dominant lethal assay after one oral dose of 150 mg/kg body. After short-term repeated exposures, dominant lethal effects were induced in mice at intraperitoneal doses from 40 mg/kg body weight (5 times per week for 3 months) and at inhalation exposures from 460 mg/m^3, (6 hours/day, 5 days per week for 11 weeks). Heritable translocations were induced in the germ cells of mice after repeated intraperitoneal exposure at doses of 30 mg/kg body weight (administered on 5 days/week over a 5-week period).

(Generoso *et al*, 1980 & 1983/WHO, 1985)

b) An abstract stated that DNA repair was induced in the germ cells of mice exposed to 540 mg/m^3 for 8 hr. The repair seemed inhibited at higher exposures.

(Cumming & Michaud, 1979/WHO, 1985)

c) Ethylene oxide has induced DNA single strand breaks in mouse sperm and spermatids, dominant lethal effects in mice and rats, chromosome aberrations in mouse spermatocytes.

(IARC 1994)

d) In two studies, male mice were exposed to ethylene oxide by inhalation under similar exposure conditions but using different mating regimens and examining different genetic events. In one study, there were no significant increases in the frequency of specific locus mutations in the offspring (Russell *et al*, 1984) while dominant visible and electrophoretically detected mutations were observed in another (Lewis *et al*, 1986).

(IARC 1994)

B.6.8.1.4.4 Summary of genotoxicity studies

Ethylene oxide is a potent mutagen in different cell lines and experimental animals. It forms DNA adducts and induces gene mutations, chromosome aberrations, cell transformation, unscheduled DNA synthesis, DNA strand breaks, sister chromatid exchanges, dominant lethal mutations and heritable translocations.

B.6.8.1.5 Long-term toxicity and carcinogenicity

Ethylene oxide has been tested in rats (1 oral and 2 inhalation studies) and in mice (2 inhalation studies, 1 topical application study and 1 subcutaneous injection study). However, since most of the studies focussed on carcinogenicity, ethylene-induced non-neoplastic effects have not been investigated extensively.

B.6.8.1.5.1 Dietary studies in rats

a) Groups of 50 female Sprague Dawley rats were orally (gavage) administered 7.5 or 30 mg/kg bw/day ethylene oxide in salad oil. The rats were dosed twice a week for 110 weeks. In addition, there were 50 vehicle controls, 50 untreated controls and 50 positive controls. No statistical analysis was reported.

The mean survival period was over 100 weeks for all groups. The mortality rate increased at 30.0 mg/kg body weight from week 100 onward. Elevated incidences of tumours were only observed in the forestomach, the first tumour appearing in week 79. The incidences of squamous cell carcinomas were 0/50, 8/50, and 29/50 at 0, 7.5, and 30 mg/kg bw/day, respectively. At 30 mg/kg bw/day, invasive growth and metastases were observed in 10 rats and 2 fibrosarcomas were also noted. At 7.5 and 30 mg/kg bw/day, the incidences of hyperplasia, hyperkeratosis, papillomas and/or carcinomas were increased in the forestomach.

(Dunkelberg, 1982/WHO, 1985)

B.6.8.1.5.2 Inhalation studies in rats

a) In a combined toxicity-carcinogenicity study, groups of 120 male and 120 female Fischer 344 rats were exposed to ethylene oxide at concentrations of 18 mg/m^3 (10 ppm), 58 mg/m^3 (32 ppm), and 173 mg/m^3 (96 ppm) for 6 hours per day, 5 day per week, over 25 months. In addition, two control groups each comprising 120 male and 120 female rats were used. There was an exposure-free period of 2 weeks in month 15, because of infection with sialoacryoadenitis virus. Interim sacrifices occurred at 6, 12, and 18 months.

The mortality rates of male and female rats increased significantly from the 22nd or 23rd month, at the highest exposure, with a trend towards an increase at a level of 58 mg/m^3. Male and female body weights were depressed at 173 mg/m^3 from the end of the first week until the end of the study. At 58 mg/m^3, the body weights of female rats were decreased between week 10 and 80.

The ophthalmologic examinations did not reveal any abnormalities.

Haematological changes were found in rats at all doses but mainly at the end of the study in animals exposed to 173 mg/m^3. These changes included an elevated leukocyte count in both sexes, a depressed red blood cell count and depressed haemoglobin values in females (some of these rats had leukaemia).

In females, the relative liver weights were increased in the 18th month at 173 mg/m^3. This effect on the liver could not be related to increases in the activities of serum alkaline phosphatase, aspartate aminotransferase, or alanine aminotransferase found

mainly at the 2 highest exposures during interim sacrifices. Relative spleen weights were increased in rats that developed leukaemia.

Non-neoplastic histopathological changes observed included an elevated frequency of focal fatty metamorphosis of the adrenal cortices in both sexes and bone marrow hyperplasia in females at 173 mg/m^3. Although no effect was observed on the hind-quarter lift reflex (examined monthly), mild skeletal muscular atrophy was observed after 2 years of exposure to 173 mg/m^3.

Neoplastic findings included increased incidences of leukaemia, peritoneal mesotheliomas, brain tumours and fibroma and the earlier appearance of pituitary tumours. A dose-related increased incidence of mononuclear cell leukaemia was found in both sexes, significant at the 2 highest exposures in females from the 18th or 19th month onwards. Trend test revealed a treatment-related response in both sexes. In males, an increased incidence of peritoneal mesotheliomas originating from the testicular mesothelium occurred at 58 and 173 mg/m^3 from the 23rd month onwards. An increased incidence of subcutaneous fibroma was seen in male rats exposed to 173 mg/m^3 that had survived for 24 months. Trend analysis showed that there was a treatment-related increase in peritoneal mesothelioma. There was no increased incidence of pituitary tumours but they appeared earlier in the 173 mg/m^3 group.

Following an increased incidence of brain tumours in Fischer 344 rats exposed to ethylene oxide (Lynch *et al*, 1984a), the brain tissue from this study was re-examined both macro- and microscopically. A dose-related incidence of primary brain tumours was observed at 58 and 173 mg/m^3 that appeared to be treatment related in the trend test but was not statistically significant. The tumours were mainly diagnosed as gliomas and malignant reticular tumours. The percentage of rats with multiple neoplasms was greater than in controls at all exposure levels in females and at 173 mg/m^3 in males. At 58 and 173 mg/m^3, the percentage of female rats with at least one malignancy was increased. It was considered that a contribution of the viral outbreak to the toxicity of ethylene oxide was unlikely.

(Snellings *et al*, 1981 & 1984b/WHO, 1985)

b) In a combined toxicity-carcinogenicity study, groups of 80 male Fischer 344 rats were exposed to ethylene oxide at concentrations of 92 mg/m^3 (51 ppm) and 182 mg/m^3 (101 ppm), for 7 hours/day on 5 days per week for 2 years. The control group also comprised 80 rats. There was an exposure-free period of 2 weeks in month 16 because of a pulmonary infection, which contributed to the mortality rate.

The mortality rate increased at both exposure levels, the increase being significant at 182 mg/m^3. At 182 mg/m^3, only 19% of the rats survived 2 years of exposure compared with 49% in the unexposed group. Body weights were reduced from the 3rd or 4th month onwards.

Serum aspartate aminotransferase activity was increased in rats exposed to 92 and 182 mg/m^3. No other changes were found in the haematological or clinical chemistry parameters.

Relative weights of the adrenal and brain were increased at both exposure levels and the relative weights of lung and kidney were increased at 92 mg/m^3.

Non-neoplastic histopathological changes included an elevated incidence of vacuolisation and hyperplasia or hypertrophy in the adrenals at both exposure levels and of atrophy and degeneration of skeletal muscle fibres at 182 mg/m^3. There were also increased incidences of inflammatory lesions of the lungs, nasal cavities, trachea and internal ear at both exposure levels. Eye cataracts developed in 2/77 (2.6%), 3/79 (3.8%) and (11.5%) at 0, 92 and 182 mg/m^3, respectively.

Neoplastic findings included increased incidences of leukaemia, peritoneal mesotheliomas and brain tumours. An increased incidence of mononuclear cell leukaemia was found which was significant at the lower exposure level. The absence of a dose-relationship was attributed to the increased mortality rate at 182 mg/m^3. Dose-related increased incidences of peritoneal mesotheliomas (originating from the testicular mesothelium) and of mixed-cell gliomas in the brain were found. The increases in both tumours were significant at 182 mg/m^3.

(Lynch *et al*, 1984a/WHO, 1985)

B.6.8.1.5.3 Inhalation studies in mice

a) B6C3F1 mice (50/sex) were exposed to ethylene oxide at concentrations of 0, 50 (92 mg/m^3) or 100 ppm (183 mg/m^3) for 6 hours/day, five days/week for 102 weeks.

No treatment-related clinical signs were reported. However, there were significant dose-related increases in the incidences of tumours. There was a dose-related increase in the incidence of alveolar/bronchiolar carcinoma [6/50, 10/50, and 16/50 in males (0/49, 1/48 and 7/49 in females) at 0, 50 and 100 ppm, respectively]. The incidences of cystadenoma in the Harderian gland were increased 1/43, 9/44, and 8/42 in males (1/46, 6/46 and 8/47 in females) at 0, 50 and 100 ppm, respectively]. In females, there were dose-related increases in the incidence of malignant lymphomas of the haematopoietic system (9/49, 6/48 and 22/49 at 0, 50 and 100 ppm, respectively) and uterine adenocarcinoma (0/49, 1/47 and 5/49 at 0, 50 and 100 ppm, respectively). The incidence of mammary adenocarcinoma and adenosquamous carcinoma combined was (1/49, 8/48 and 6/49 at 0, 50 and 100 ppm, respectively.

(US National Toxicology Program, 1987/IARC 1994 & ECHC 2001)

b) Female A/J mice (considered to be highly susceptible to lung tumours) were exposed to ethylene oxide at concentrations of 128 and 366 mg/m^3 for 6 hours/day, 5 days/week, for 6 months. A dose-related increase in pulmonary adenomas was observed (only lungs examined).

(Adkins *et al*, 1986/ECHC 2001)

B.6.8.1.5.4 Other studies in mice

a) Subcutaneous exposure

Groups of 100 female NMRI mice were injected once a week with a tricaprylin solution containing 0.1, 0.3, or 1.0 mg ethylene oxide per animal, for 106 weeks. There were 200 vehicle controls and 200 untreated controls. From week 35 to week 85, the mortality rate increased by a maximum of 10% at a dose of 1.0 mg per mouse. The mean length of survival in this group was 75 weeks. An elevated incidence of tumours was only observed at the injection site, the first tumour appearing in week 79. There was a dose-related increased incidence of sarcomas, mainly fibro sarcomas, which was significant at 0.3 and 1.0 mg per mouse. The tumour incidence was 11% at the highest dose compared with 2% in vehicle controls.

(Dunkelberg, 1981/WHO, 1985)

b) Dermal exposure

Each of a group of 30 female Swiss Millerton mice received, for their lifetime, approximately 100 mg of a 10% solution of ethylene oxide (purity 99.7%) in acetone, brushed on the clipped dorsal uncovered skin, 3 times a week. A group of 60 mice did not receive any treatment and a group of 60 mice received the vehicle only. Skin tumours were not found, nor were there any sign of skin irritation. The median length of survival was 493 days for treated mice and 445 days for controls. It is assumed that ethylene oxide, applied in this manner, evaporated rapidly from the skin.

(Van Duuren *et al*, 1965/WHO, 1985)

B.6.8.1.5.5 Summary of chronic toxicity/carcinogenicity

Chronic toxicity

The main emphasis of the available chronic investigations was focussed on the carcinogenic activity of ethylene oxide. There are limited information/data on the non-neoplastic effects of ethylene oxide.

In rats, the mortality rate and the incidences of hyperplasia and hyperkeratosis in the forestomach was increased following oral exposure. Following inhalation exposure, the mortality rate was increased, body weights decreased, inflammatory lesions of the lungs, nasal cavities, trachea and internal ear were increased and the development of eye cataracts. The haematological changes included elevated leukocyte counts in both sexes. In addition, bone marrow hyperplasia, depressed red blood cell counts and haemoglobin values were seen in females. Serum aspartate aminotransferase activity was increased. The relative weight of several organs was increased (brain, liver, lung, kidneys and adrenals). The microscope changes in the adrenals included an increased frequency of focal fatty metamorphosis, vacuolisation and hyperplasia or hypertrophy in the adrenals and atrophy and degeneration of skeletal muscle.

Chronic non-neoplastic investigations in mice are not reported.

Carcinogenicity

Following oral exposure, a dose-related increase in the incidence squamous cell carcinomas in the forestomach was reported in rats at 7.5 & 30 mg/kg bw/day (invasive growth and metastases were also reported at the high dose).

Following inhalation exposure, there were significant dose-related increases in several tumour types of tumours in rats (leukaemia, peritoneal mesotheliomas, brain tumours and subcutaneous fibroma) and mice (alveolar/bronchiolar carcinoma, malignant lymphomas of the haematopoietic system, uterine adenocarcinoma and mammary adenocarcinoma and adenosquamous carcinoma). It is also noteworthy that pituitary tumours appeared earlier in rats and that an increase in lung tumours was reported in mice after only 6 months of exposure.

Following subcutaneous injections to mice, there was a dose-related increased incidence of sarcomas, mainly fibro sarcomas, at the injection sites. No skin tumours (or skin irritation) were found in mice after long-term dermal exposure but it was assumed that ethylene oxide evaporated rapidly from the skin.

Overall conclusions

The extensive evidence of genotoxicity (*in vitro* and *in vivo* effects) and carcinogenicity (a variety of tumours in rats and mice and the evidence of the early appearance of certain tumours in rats and mice) indicates that ethylene oxide is a potent genotoxic carcinogen in experimental animals. A NOAEL for ethylene oxide-induced tumours cannot be established for oral or inhalation exposure. The non-neoplastic effects of ethylene have not been fully investigated but appear to occur at dose levels above tumour induction.

B6.8.1.6 Reproductive toxicity

No reproductive studies using oral administration were submitted (or cited from the published literature). The following studies used inhalation exposure.

B.6.8.1.6.1 Multigeneration studies in rats (IIA 5.6.1)

a) Fischer 344 rats (30/sex) were exposed to ethylene oxide at concentrations of 18, 58 or 173 mg/m^3, for 6 hours/day, 5days per week, over 12 weeks. Two control groups of 30 rats per sex each exposed to air only. After mating, females were further exposed for 7 days/week for up to three weeks after delivery with the exception of the first 5 days of lactation. The percentages of pregnant females and fertile males were not affected by ethylene oxide exposure. The number of pups per litter, the number of implantation sites per female and the number of foetuses born per implantation site were decreased at 173 mg/m^3. In addition, the number of females with a gestation period longer than 22 days was also increased at this concentration but no effects were noted on the average length of the gestation period. Neither parents nor pups showed signs of toxicity from ethylene oxide.

(Snellings *et al*, 1982a/WHO, 1985)

B.6.8.1.6.2 Developmental toxicity studies (IIA 5.6.2)

Developmental studies in rats

a) Groups of Sprague Dawley rats (32-45 females) were exposed to ethylene oxide at concentrations of 0 or 270 mg/m^3 for 7 hours/day. They were exposed on days 7-16 of gestation (Group 1) or on days 1- 16 of gestation (Group 2) or during 3 weeks before mating (5 per week) and on days 1 - 16 of gestation (Group 3).

No dams died during the study but body weights were decreased in Group 3. In all exposed groups, the relative and absolute weights of kidney and spleen were increased. The results of histopathological examination did not show any abnormalities. There was a significant increase in resorptions per litter and per implantation site in Group 3 but no significant effects on the number of implants, live foetuses or pregnancies. In all exposed groups, the weights and the lengths of the foetuses were decreased. Reduced ossification of sternebrae and skull was observed.

(Hackett *et al*, 1982/WHO, 1985)

b) Groups of Fischer 344 rats (22 females) were exposed to ethylene oxide at concentrations of 18, 58, or 173 mg/m^3, for 6 hours/day on days 6-15 of gestation. Two control groups comprising 22 rats each were exposed to air only. The numbers of pregnant dams ranged from 17 to 22. Maternal behaviour was normal, and there were no deaths. The only effect on the foetuses was a 5-8% decrease in weight at 180 mg/m^3.

(Snellings *et al*, 1982b/WHO, 1985)

Developmental studies in mice

a) Groups of CD-1 mice (24-37 females) each received intravenous injections of ethylene oxide at doses of 0, 75 or 150 mg/kg bw in an aqueous dextrose solution on days 4-6, 6-8, 8-10 or 10-12 of pregnancy.

Dams exposed on days 6-8 of pregnancy did not show toxic signs but there was a 20% decrease in foetal weight. In all the other groups at the top dose, clinical signs of toxicity were observed and included increased mortality (19-48%), weakness, laboured respiration and tremor. Foetal malformations were shown in 19.3% of foetuses in exposed litters compared with 2% in control groups. These malformations were mainly fused cervical arches. In addition, fused thoracic arches, scrambled and fused sternebrae and fused, branched, or missing thoracic ribs were observed.

(Laborde & Kimmel, 1980/WHO, 1985)

b) Exposure of F1 female mice (C3H x C57B1 or SEC x C57B1) mated with F1 males (C3H x C57B1) to ethylene oxide at a concentration of 2196 mg/m^3 for 1.5 hours could produce different results depending on the timing of exposure. Females were exposed at 1, 6, 9 or 25 hours after timed 30 minute matings. These time intervals correspond to time of sperm penetration, early pronuclear stage (before DNA synthesis), pronuclear DNA synthesis and early two-cell stage, respectively. It was noted that maternal toxicity was not reported despite the high concentrations used.

Exposure at 1 or 6 hours increased the number of mid-gestational and late foetal deaths but few effects were seen after 9 hours and none were seen after 25 hours. A large proportion of the foetuses that survived after exposure at 6 hours had a range of congenital malformations including omphalocoele, hydropia, open thorax, and limb and tail defects (37% *versus* 2% in controls). Malformations were also seen in foetuses exposed at 1 hour but not those exposed at 9 or 25 hours. In a later study, with identical exposure protocols but more detailed foetal examination, an increased incidence of malformations was found after exposure at 1, 6, 9 and 25 hours. Other females exposed to ethylene oxide for up to 14 days before mating had mainly an increase in early embryonic death around the time of implantation, probably as a result of dominant lethal mutations.

(Generoso *et al*, 1987; Rutledge and Generoso, 1989/IARC 1994)

Developmental studies in rabbits

New Zealand rabbits were exposed to ethylene oxide at a concentration of 270 mg/m^3 from days 1-19 or from days 7-19 of gestation. There was no evidence of toxicity in the mothers, embryos, or foetuses, or of any developmental defects.

(Hackett *et al*, 1982/WHO, 1985)

B.6.8.1.6.3 Effects on sperm and reproductive tissues/organs

a) Wistar rats (12 or 6 males/dose) were exposed to ethylene oxide at concentrations of 0, 91.5, 183, or 457.5 mg/m^3 for 6 hours/day on fine days/week for 13 weeks. At 457.5 mg/m^3, epididymal but not testicular weight was reduced, there was slight degeneration in some seminiferous tubules, a reduced sperm count in the body and tail but not the head of the epididymus and an increase in sperm head abnormalities due mainly to the presence of immature sperm. An increase in malformed sperm heads unrelated to dose was observed in all treated groups over that in control (15% *versus* 2%).

(Mori *et al*, 1991/IARC 1994)

b) Male Cynomolgus monkeys were exposed to ethylene oxide at concentrations of 0, 90 or 180 mg/m^3 for 7 hours/day on 5 days/week for 2 years. A decline in sperm count and mobility was observed at both dose levels but the incidence of abnormal sperm heads did not change.

(Lynch *et al*, 1984c/WHO)

B.6.8.1.6.4 Summary of reproductive toxicity

No data/information has been submitted (or cited from the literature) on the reproductive toxicity of ethylene oxide via the oral exposure route. However, there are sufficient data/information generated by studies using inhalation exposure to establish that ethylene oxide is a reproductive toxin that affects fertility and development in experimental animals (some effects are evident in the absence of maternal toxicity). In mice, there is clear evidence of teratogenic activity after intravenous injections and evidence that mutagens can induce foetal malformations and death when administered around the time of fertilisation. Sperm abnormalities have been reported in rats and monkeys following inhalations exposure to ethylene oxide.

B.6.8.1.7 Neurotoxicity studies

No specific neurotoxicity studies have been submitted (or cited from the literature). All the reported effects of ethylene oxide on the nervous system in experimental animals have been observed and reported in standard repeat-dose inhalation studies.

B.6.8.1.7.1 Repeat dose neurotoxicity studies

a) In a limited, poorly reported study in rabbits and monkeys, paralysis of the hind limbs was observed in both species accompanied by atrophy of the leg muscles, following exposure to ≥ 370 mg/m^3 for periods ranging from 7 to 32 weeks (exact exposure periods were not clearly specified).

(Hollingsworth *et al*, 1956/ECHC, 2001)

b) In sub chronic or chronic studies, in rats exposed to ethylene oxide a concentrations between 458-915 mg/m^3 there was a range of neurological effects including awkward or ataxic gait, paralysis and atrophy of the muscles of the hind limbs, accompanied in some cases by pathological evidence of axonal degeneration of myelinated fibers in nerves of the hind legs.

(Hollingsworth *et al*, 1956 & Other workers/ECHC, 2001)

c) Poor coordination of the hind quarters was observed in rats and mice following exposure to ethylene oxide at 810 mg/m^3 for 7-8 weeks.

(Snellings *et al* 1982/ECHC, 2001)

d) Abnormal posture during gait and reduced locomotor activity were also observed in mice after exposure to ethylene oxide at concentrations ranging from 86 to 425 mg/m^3, for 6 hours/day on 5 days/week for 10 or 11 weeks. Effects on various reflexes (righting, tail pinch, toe pinch) were also noted at the highest concentration examined.

(Snellings *et al* 1984a/ECHC, 2001)

e) In two studies of male cynomolgus monkeys exposed to ethylene oxide at concentrations of 92 or 183 mg/m^3 for 2 years, histological alterations in the axons within the nucleus gracilis of the medulla oblongata and demyleination of the fasciculus gracilis within the medulla were observed.

(Sprinz *et al*, 1982/Lynch *et al*, 1984b/ECHC, 2001)

B.6.8.1.7.2 Summary of the neurotoxicity studies

There is no data/information on the neurotoxicity of ethylene oxide via the oral exposure route. There is sufficient data/information generated by studies using inhalation exposure to establish that ethylene oxide is a neurotoxin in experimental animals.

B.6.8.1.8 Other toxicological data/information

B.6.8.1.8.1 Mode of action

Ethylene oxide is an electrophilic agent that alkylates nucleophilic groups in biological macromolecules, i.e. including DNA and protein (e.g. haemoglobin & albumin). It is considered likely that the toxicological effects of ethylene oxide arise primarily from the direct alkylation of macromolecules.

Since ethylene oxide is formed during the metabolism of ethylene (a natural body constituent) both endogenous and exogenous sources of ethylene and ethylene oxide will contribute to the background alkylation of macromolecules.

(CICADS 54, 2003 & IARC 1994)

B.6.8.1.8.2 Ethylene oxide detected in food stuffs and cosmetics and on medical devices

a) Ethylene oxide was detected in 96 of 204 (47%) samples of food products taken from retail stores in Denmark in 1995 (Jensen, 1988). The reported concentrations reflect the total amount of ethylene chlorohydrin and ethylene oxide present at the time of analysis. These concentrations ranged from <0.05 to 1800 mg/kg in the individual samples without correction for recoveries. Ethylene oxide was detected frequently among 24 samples of spices at a mean concentration of 84 µg/g and a maximum concentration of 580 µg/g.

(Jensen, 1988/ECHC 2001)

b) Ethylene oxide was detected, but not quantified, in 1 of 2372 samples of eggs and in 1 sample of 3262 samples of fish collected in the United States in 19975 as part of the Food and Drug Administration Monitoring Program (1970-1976).

(Duggan *et al*, 1983/ECHC 2001)

c) Ethylene oxide may be present as a contaminant of skin care products. Current commercial preparations of polyglycol ethers may contain residues of ethylene monomer up to approximately 1 µg/g.

(Filser *et al*, 1994/ECHC 2001)

d) Ethylene oxide monomer in skin care products have been reported at 1.9 to 34 $nmol/cm^3$ (0.08 to 1.5 mg/l) and a range of maximum skin penetration of ethylene oxide of 1-14% in various product formulations.

(Kreuzer, 1992/ECHC 2001)

e) Ethylene oxide may be absorbed by medical equipment during sterilization and may remain there as unchanged compound or as one of its reaction products (WHO, 1985). Studies show that residual concentrations of ethylene oxide in medical equipment immediately following their sterilization have ranged up to 1 or 2%. These concentrations generally declined rapidly after a few days aeration, although levels exceeding 100 ppm (183 mg/m^3) were sometimes measured following aeration.

(Gillespie *et al*, 1979 & 1980/ECHC 2001)

B.6.8.1.9 Human data/information

B.6.8.1.9.1 Absorption, distribution, metabolism and excretion

a) Ethylene oxide is very soluble in blood and readily taken up by the lungs; approximately 20-25% of inhaled ethylene oxide reaching the alveolar space is exhaled as unchanged compound and 75-80% is taken up by the body and metabolised. The half-life in the body has been estimated to be less than 1 hour.

(Brugnone *et al*, 1986; 1988; Filser *et al*, 1992/IARC 1994)

b) Pharmacokinetic data obtained form experimental animals to calculate the internal dose of ethylene oxide in man obtained from daily exposure. For a man exposed for 8 hours to ethylene oxide at 1 ppm (1.8 µg/litre), the area under the concentration-time curve in blood plasma was estimated to be 18.8 µg/hour/ml on the basis of data for rats and 14.3 µg/hour/ml on the basis of dog data.

(Beliles and Parker, 1987/IARC 1994)

c) The blood concentrations of ethylene glycol were in sterilisation personnel exposed to ethylene oxide. The mean concentrations of ethylene glycol in blood in exposed worker (90 mg/litre) were twice that in unexposed workers (45 mg/ml).

(Wolfs *et al*, 1983; Brown *et al*, 1996 & Other workers/IARC 1994)

d) The concentration of thioesters excreted in urine collected from sterilisation workers at the end of sterilisation processes was twice that in non-smoking personnel.

(Burgaz *et al*, 1992/IARC 1994)

e) *In vitro* investigations suggest that the human population can be divided into conjugators (75%) and non-conjugators (25%) based on enzymic conjugation of ethylene oxide with glutathione in erythrocytes.

(Hallier *et al*, 1993/IARC 1994)

f) Ethylene oxide is an electrophilic agent that alkylates nucleophilic groups in biological macromolecules, e.g. DNA and haemoglobin. There are numerous published studies that have investigated the formation nitrogen adducts (hydroxethyl adducts of valine, cysteine and histidine) in the haemoglobin of workers occupationally exposed to ethylene oxide. Ethylene oxide binding to DNA primarily results in the formation 7-(2-hydroxethyl) guanine adducts but other adducts have been identified at lower levels. DNA extracted from lymphocytes of unexposed individuals had mean background levels of 7-(2-hydroxethyl) guanine that ranged between 2-8.5 pmol/mg DNA. It has been reported that human tissue contains 10- to 15-fold higher levels of endogenous 7-(2-hydroxethyl) guanine adducts than rodents.

(Bolt, 1996; Bolt *et al*, 1997; Wu et al, 1999a/CICADS 2003)

g) Ethylene oxide is metabolised by hydrolysis to ethylene glycol and conjugation with glutathione (both are considered to be detoxification pathways). The hydrolysis pathway predominates in larger species such as the rabbit and dog while the conjugation pathway predominates in rodents. A physiologically based pharmacokinetic (PBPK) model for the dosimetry of inhaled ethylene oxide has calculated that 80%, 60% and 20% would be metabolized via glutathione conjugation in mice, rats and humans, respectively. This appears to be consistent with the levels of glutathione S-transferase enzyme (GSTT1) activity (mice>rats>humans); ethylene oxide is a substrate for the human GSTT1 enzyme. Higher levels of haemoglobin adducts have been reported in exposed individuals (workers and smokers) with the GSTT1 'null genotype' (homozygous deletion of the GSTT1 gene) than among those with a GSTT1 'positive genotype' (at least one copy of the GSTT1 gene).

(Yong *et al*, 2001; Fennell and Brown, 2001; Pemble *et al*, 1994/CICADS 2003)

h) Reports on two PBPK models for ethylene oxide in rodents and humans indicate that ethylene oxide is a direct acting alkylating agent in humans and rodents via the same mode of action (i.e. the quantitative differences between humans and rodents result from differences in basic physiology rather than mode of action).

(Csandy *et al*, 2000; Fennel and Brown 2001; Pemble *et al*, 1994/CICADS 2003)

B.6.8.1.9.2 Acute toxicity, skin and eye irritation and sensitisation

a) Five sterilizer operators were exposed accidentally to ethylene oxide at concentrations high enough to be smelt (odour threshold 1280 mg/m^3) for periods up to 0.5 hours. Two operators suffered headache and diarrhoea which resolved after about 70 hours. Three operators suffered irritation of the eyes and throat, mouth dryness, pruritus, headache, vertigo, myasthenia, indigestion and haemolysis which had resolved within 21 days of the exposure. Haemolysis diagnosed on days 9-11 lasted until day 16.

(Deleixhe *et al*, 1986/IARC 1994)

b) Acute effects on the nervous system in nearly all inhalation cases were marked by nausea, recurrent vomiting, and headache. Less frequently reported effects included decreased consciousness (one case of coma), excitement, sleeplessness, muscular weakness, diarrhoea, and abdominal discomfort.

(Capellini and Ghezzi, 1965 and Other workers/WHO, 1985)

c) Accidental skin exposure to a 1% aqueous solution, from the waist down, was reported to result in effects on the nervous system (nausea and repeated vomiting).

(Sexton and Henson, 1949/WHO 1985)

d) Burns on the hands were attributed to gloves containing residual traces of ethylene oxide used for sterilization. Mild skin irritation has been reported after exposure to 1% aqueous solutions of ethylene oxide. Dermal irritation is characterised by erythema, oedema and the formation of vesicles and has been observed after contact with ethylene oxide-sterilized materials and clothing.

(Fisher, 1988/IARC 1994)

e) Skin and eye irritation in sterilizer operators were associated with exposures to ethylene oxide at concentrations up to 19.6 mg/m^3.

(Bryant *et al*, 1989/IARC 1994)

f) Exposure to ethylene oxide can cause irritation of the mucous membranes of the respiratory passages.

(Thiess, 1963/ECHC 2001)

g) Ethylene oxide is a sensitising agent. Type I (mild to severe anaphylactic reactions) and Type IV (contact dermatitis) hypersensitivity reactions have been observed in patients who received dialysis treatment with equipment that had been sterilized with ethylene oxide.

(Bommer and Ritz, 1987/IARC)

h) Severe respiratory problems due to inflammatory reactions in the trachea and larynx were reported inpatients who had received endotracheal intubation with tubes sterilised with ethylene oxide.

(Mantz *et al*, 1972 and Other workers/WHO 1985)

B.6.8.1.9.3 Genetic effects

Numerous studies have shown that ethylene oxide induces chromosome aberrations, micronuclei and sister chromatid exchanges in humans and the extent of the damage is related to the level and duration of exposure.

a) Increased incidences of sister chromatid exchange have been reported in peripheral blood lymphocytes of hospital sterilisation workers exposed to 1 ppm ethylene oxide (8 hour TWA) and concentrations between 0.5-25 ppm for various durations.

(Yager *at al*, 1983; Stolly *et al*, 1984; Tates *et al*, 1991a/IARC 1994)

b) Increased incidences of chromosome aberrations have been reported in lymphocytes of sterilisation workers. It has been stated that ethylene oxide exposures above 9 mg/m^3 are required to induce chromosome aberrations.

(Galloway *at al*, 1986/IARC 1994)

c) Increased incidences of micronuclei have been reported in factory workers, i.e. in lymphocytes at concentrations of 25-720 9 mg/m^3, in erythroblasts and polychromatic erythrocytes in bone marrow samples at a concentration of 1 ppm for 0.5 to 8 years and in exfoliated nasal mucosa cells following accidental exposures.

(Tates *at al*, 1991a; Hodstedt *et al*, 1983; Sarto *et al*, 1990/IARC 1994)

d) Mutations at the HPRT locus in circulating lymphocytes of factory workers have been reported in one study.

(Tates *at al*, 1991b/IARC 1994)

B.6.8.1.9.4 Neurological effects

a) Several studies in sterilizer operators have associated ethylene exposure with symptoms of peripheral and central neurotoxicity. In cases of peripheral neuropathy, the symptoms included numbness in feet and fingers, muscular weakness in the lower limbs, a reduction in sural nerve velocity, nerve fibre degeneration, and demyelination. Central nervous system effects were implied on the basis of personality dysfunction and cognitive impairment.

(Schroder *et al*, 1985 and Other workers/IARC)

b) Because of a leaking sterilizer, 4 young men were exposed intermittently, for 2-8 weeks, to ethylene oxide at levels of approximately 1000 mg/m^3. Three of the men developed a reversible peripheral neuropathy showing abnormal nerve conduction and, in 2 cases, headache, weakness and decreased reflexes in the extremities, incoordination, and a wide-based gait. The fourth man developed a reversible acute encephalopathy with headache, nausea, vomiting, lethargy, recurrent motor seizures, agitation and a diffusely slow electroencephalogram. Following this, 6 more cases were reported concerning sterilizer operators, suffering from reversible peripheral neuropathy following ethylene oxide exposure for 0.5-1.5 years.

(Gross *et al*, 1979/WHO 1985)

c) Three people exhibited subacute polyneuropathy with bilateral foot-drop, slowing of nerve conduction velocity and enervation potential on electromyography as the main findings. All 3 people had noticed the smell of ethylene oxide regularly at work while 2 persons experienced eye irritation.

(Finelli *et al*, 1983/WHO 1985)

d) Polyneuropathy was also reported in 3 sterilizer operators. Two of these cases were described in detail. Sural nerve biopsies revealed axonal degeneration with mild changes in the myelin sheath and unmyelinated fibres were also involved. Muscle biopsies showed typical denervation atrophy.

(Kuzuhara *et al*, 1983/WHO 1985)

B.6.8.1.9.5 Reproductive effects

a) The rate of spontaneous abortions was significantly higher ($P<0.05$) in Finish hospital workers associated with ethylene oxide exposure (20.4%) than in controls (11.3%). Randomly selected Californian dental assistants (aged 18-39) examined for the occurrence of spontaneous abortion and pre- (27-37 weeks) and post-term births ($\geq$ 42 weeks) in relation to ethylene oxide exposure. Ethylene exposed women were stated to be 2.7 times more likely to have any of the three adverse effects after adjusting for age.

(Hemminki *et al*, 1982; Rowland *et al*, 1996/CICADS 2003)

b) One paper reported an increased risk of spontaneous abortion in Finish women whose partners had been exposed to ethylene oxide. Paternal exposure was based upon the job and industry in which the men were employed (no quantitative exposure data). The number of spontaneous abortions (n=3) and pregnancies (n=10) in the paternal group was small and confounding factors, such as previous abortions, alcohol and tobacco consumption were not considered in the analysis.

(Lindbolm *et al*, 1991/CICADS 2003)

B.6.8.1.9.6 Occupational exposure

a) The health status of 37 male operators from an ethylene oxide-producing plant in the USA during the period 1953-62 was compared with that of age-matched operators from other production units. The average employment period was 11 years for exposed workers and 12 years for controls. The usual average exposure level was between 9 and 18 mg/m^3 with occasional peaks up to 230 mg/m^3 for one particular job (collecting a sample of the product). According to the medical records, the health of the exposed workers was somewhat better than that of the controls. A physical examination and extensive clinical tests did not reveal any exposure-related effects with the exception of a slightly increased white blood cell count.

(Joyner, 1964/WHO 1985)

b) Chromosomal damage was found in a group of 12 workers from a hospital sterilization facility in the USA. The maximum exposure concentration measured during sterilization was 65 mg/m^3. Another group of 12 persons, who worked in the adjacent operating room area, volunteered as representatives of an unexposed or accidentally exposed group. To ensure adequate control throughout the study, unexposed laboratory staff members served as a third group. Frequently-reported subjective complaints indicated irritation of the mouth, throat, and eyes, and effects on the nervous system, such as headache, nausea, speech difficulty, memory loss, dizziness and incoordination.

(Garry *et al*., 1979/WHO 1985)

c) In Belgium, a group of 18 workers, using or distributing the sterilant ethylene oxide, were compared with a well-matched control group by means of a questionnaire, and by analyses for urinary retinol-binding protein and albumin, beta-microglobulin, and chromosomal damage in lymphocytes. The overall mean exposure level was 7.6 mg/m^3 and the time-weighted average exposure, over a working day, ranged between 0.2 and 95 mg/m^3. A significant increase in the incidence of sleeplessness and leg

cramps was recorded, but not irritation or allergy. These studies did not reveal any abnormalities with the exception of an increase in sister chromatid exchanges in lymphocytes.

(Wolfs *et al*, 1983; Laurent *et al*, 1984/WHO, 1985)

d) In a plant in Bulgaria, 196 workers engaged in the production of ethylene and ethylene oxides were examined. About 73% of all concentrations of ethylene oxide measured were 1 mg/m^3 or less while 27% were between 1 mg/m^3 and 3.5 mg/m^3. Significant increases were found in deviations of the autonomous nervous system and in neurosis-like manifestations, especially in female workers but woman may be more prone to neuroses. Because of a mixed exposure was difficult to evaluate the findings.

(Spasovski *et al*, 1980/WHO, 1985)

e) Haematological changes were reported in a group of 27 workers in an ethylene oxide manufacturing and processing plant, in Sweden, in 1967. The exposure period varied from 2 to 20 years, the average length being 15 years. Controls worked with ethylene oxide in other departments where no leakages were likely. No exposure data were reported. When 2 cases of anaemia were excluded, there was still a significantly decreased haemoglobin value in exposed workers. There was a 30% increase in the number of lymphocytes, and one case of chronic lymphatic leukaemia was noted in the exposed workers.

(Ehrenberg & Hallstrom, 1967/WHO, 1985)

f) In the Federal Republic of Germany, 279 employees from 8 plants in which alkene oxides were produced or processed, were examined for morbidity during 1978. They were employed for an average of 10.8 years. Of these workers, 21 had been involved in accidents with ethylene oxide. Taking into account age and length of exposure, they were compared with groups of industrial and clerical workers within the same company. No abnormalities were found that could be related to ethylene oxide or propylene oxide. Lymphocytosis and increases in haemoglobin and erythrocyte volume were attributed to age or smoking. The exposure concentrations were not reported. The workers were also exposed to many other chemicals, some of which may be carcinogenic for man.

(Stoker & Thiess, 1979/WHO, 1985)

g) Haematological effects were observed among a group of 59 women exposed to ethylene oxide released from sterilizers while employed in nine hospitals in the USA and one hospital in Mexico. Compared with unexposed controls, US workers (exposed to a mean 8-hour TWA exposure of 0.31 mg/m^3 with a range of 0.24-0.55 mg/m^3) exhibited a statistically significant increase in the percentage of lymphocytes and a reduction in the percentage of neutrophils in the blood). No statistically significant effects were found in Mexican workers.

(Schulte *et al*, 1995/CICADS 2003)

h) Haematological effects were not observed in a group of 84 male workers involved in the manufacture of ethylene oxide and exposed to estimated concentrations of <1.83 mg/m^3.

(Currier *et al*, 1984/CICADS 2003)

i) Haematological effects were not observed in a group of 36 male workers involved in the manufacture of ethylene oxide with estimated 8-hour TWA exposures below 0.09 mg/m^3.

(van Sittert *et al*, 1985/CICADS 2003)

j) A study in 46 Israeli hospital workers exposed (at three locations with a mean period of employment of 6.6 years) to 145- to 210 minutes TWA concentrations of <0.02-0.1 mg/m^3 found statistically significant haematological effects compared to 88 non-occupational exposed controls (matched for age, sex and smoking habits). There were increases in the absolute mean numbers of erythrocytes, monocytes and eosinophils, increases in the haematocrit and reductions in the absolute mean numbers of lymphocytes and platelets.

(Shaham *et al*, 2000/CICADS 2003)

k) Lens opacities and cataracts were assessed in French hospital workers exposed to ethylene oxide at concentrations of 0.11 mg/m^3 during a 97-minute exposure to 71 mg/m^3 during a 2.5 minute exposure. There were no differences between the exposed and control groups in the case of lens opacities. However, cataracts were observed in six exposed people compared to none in the controls (lens opacities have been reported in monkeys exposed to 100 ppm for up to 24 months).

(Deschamps *et al*, 1990/CICADS 2003)

l) Following accidental exposure (4 hours/day for 4 days), to concentrations of ethylene oxide high enough to be smelt, one worker out of five developed persistent non-immunological asthma, probably induced by extensive epithelial injury which lead finally to fibrosis (no further information on the outcome).

(Deschamps *et al*, 1992/IARC 1994)

B.6.8.1.9.7 Case and epidemiological studies

Numerous summaries of case and epidemiological studies are presented in the submitted publications (IARC 1994, ECHC 2001 & CICADS 2003).

In epidemiological studies, the most frequently reported association in workers exposed to ethylene oxide has been with lymphatic and haematopoietic cancer. The workers studied fell mainly into two groups: i) people using ethylene oxide as a sterilant, ii) chemical workers manufacturing (either by the chlorohydrin process or more recently by the catalytic oxidation of ethylene) or using the compound in other processes. In general, people involved in sterilization are less likely to have occupational exposure to other chemicals.

B.6.8.1.10 Summary and conclusions

Ethylene oxide is an electrophilic agent. It is considered likely that the toxicological effects of ethylene oxide arise primarily from the direct alkylation of macromolecules (e.g. DNA and proteins).

The majority of data for ethylene oxide has been primarily generated using the inhalation exposure route. Only limited data are available for ethylene oxide administered via the oral route.

Oral exposure

The acute oral LD50 values for ethylene oxide were stated to be 330 mg/kg bw for male rats and 365 and 280 mg/kg bw for male and female mice, respectively. In a subacute rat study, the findings included loss of body weight, gastric irritation and slight liver damage. The only long-term rat study (gavage dosing) reported a dose-related increase in the incidence of squamous cell carcinomas in the forestomach at all dose levels tested.

Other routes of exposure (primarily inhalation exposure)

Ethylene oxide is very soluble in blood and the pulmonary absorption is expected to be rapid and extensive. Excretion is also rapid and occurs mainly via urine while minor amounts of unchanged parent and labelled carbon dioxide are excreted via the lungs. Distribution is widespread based on the protein and DNA adducts in various organs and tissues. Two metabolic pathways have been identified, the hydrolysis of ethylene oxide to 1,2-ethanediol and conjugation with glutathione to produce S-(2-hydroxyethyl)cysteine and N-acetyl- S-(2-hydroxyethyl)cysteine.

Following acute exposure to ethylene oxide, the respiratory system, the nervous system and the liver and kidneys were identified as target organs. Ethylene oxide is a potent eye, skin and respiratory irritant and a sensitiser.

In the short-term studies, mortalities and effects on respiratory system, the haematological system (including bone marrow), the nervous system, ocular lens, liver and kidneys, thymus and spleen and the testes were reported. A dose-related in crease in pulmonary adenoma was also seen in mice after 6 mounts of exposure.

Ethylene oxide is an alkylating agent and is considered to be a mutagen in experimental animals and humans. It forms DNA adducts and induces gene mutations, chromosome aberrations, cell transformation, unscheduled DNA synthesis, DNA strand breaks, sister chromatid exchanges, dominant lethal mutations and heritable translocations.

The chronic findings in rats included deaths, reduced body weight, inflammatory lesions of the lungs, nasal cavities, trachea and internal ear and the development of eye cataracts. There were several reports of haematological changes (including bone marrow changes) and changes in some serum enzyme activities. Organ weight changes were also reported. The microscopic findings included lesions in the adrenals

and atrophy and degeneration of skeletal muscle. No chronic non-neoplastic findings in mice were reported.

Dose related neoplastic changes were evident in rats and mice following long-term inhalation exposure. There were significant dose-related increases in several tumour types of tumours in rats (leukaemia, peritoneal mesotheliomas, brain tumours and subcutaneous fibroma) and mice (alveolar/bronchiolar carcinoma, malignant lymphomas of the haematopoietic system, uterine adenocarcinoma and mammary adenocarcinoma and adenosquamous carcinoma). It is also noteworthy that pituitary tumours appeared earlier in rats and that an increase in lung tumours was reported in mice after only 6 months of exposure.

Following subcutaneous injections to mice, there was a dose-related increased incidence of sarcomas at the injection sites. No skin tumours (or skin irritation) were found in mice after long-term dermal exposure but it was assumed that ethylene oxide evaporated rapidly from the skin.

The extensive evidence of genotoxicity (*in vitro* and *in vivo* effects) and carcinogenicity (a variety of tumours in rats and mice and the evidence of the early appearance of certain tumours in rats and mice) indicates that ethylene oxide is a potent genotoxic carcinogen in experimental animals.

In the rat multigeneration study, there were reductions in the number of pups per litter, the number of implantation sites per female and the number of foetuses born per implantation site and an increase in the length of the gestation period. An increase in resorptions per litter and per implantation site were also noted in the rat developmental study together with reduced foetal weight and length and reduced ossification of sternebrae and skull was observed. In mice, there is clear evidence of teratogenic activity (severe skeletal malformations) after intravenous injections and evidence that mutagens can induce foetal malformations and death when administered around the time of fertilisation. Effects on sperm and reproductive tissues have been reported in rats and monkeys. There are sufficient data/information to establish that ethylene oxide is a reproductive toxin that affects fertility and development in experimental animals (some effects are evident in the absence of maternal toxicity).

There are numerous reports of adverse neurotoxicity in a range of experimental animals that include effects on reflexes, reduced locomotor activity, ataxia, limb paralysis, muscle atrophy, axonal degeneration in the limbs and histological alterations of the medulla oblongata of primates.

The data base for ethylene oxide in rodents and humans indicate that ethylene oxide is a direct acting alkylating agent in humans and rodents via the same mode of action (i.e. the quantitative differences between humans and rodents result from differences in basic physiology rather than mode of action).

There are numerous reports of ethylene oxide-induced effects in humans/workers and include irritation of the eyes, skin and throat, mouth dryness, pruritus, headache, vomiting, vertigo, myasthenia, indigestion, diarrhoea and haemolysis. Less frequently reported effects included decreased consciousness (one case of coma), excitement, sleeplessness, muscular weakness, diarrhoea, and abdominal discomfort. Ethylene

oxide is also a sensitising agent and induces Type I (mild to severe anaphylactic reactions) and Type IV (contact dermatitis) hypersensitivity reactions and inflammatory reactions in the trachea and larynx.

Occupational exposures to ethylene oxide have resulted in reports of a wide range of serious adverse effects that include haematological effects, a possible increase in ocular lens cataracts, symptoms of peripheral and central neurotoxicity, increases in chromosome aberrations, micronuclei and sister chromatid exchanges and spontaneous abortions. In addition, ethylene oxide exposure of workers has frequently been associated with lymphatic and haematopoietic cancer.

In 1994, IARC concluded that there was limited evidence in humans for the carcinogenicity but there was sufficient evidence in experimental animals for the carcinogenicity of ethylene oxide. The overall conclusion of IARC 1994 was that ethylene oxide is carcinogenic to humans (Group 1) when the following evidence was taken into consideration.

Ethylene oxide is a directly acting alkylating agent that:

i) persistently induces dose-related increases in the frequency of chromosome aberrations and sister chromatid exchange in lymphocytes and micronuclei in bone marrow cells of workers;

ii) has been associated with malignancies of the lymphatic and haematopoietic system in humans and experimental animals;

iii) induces dose-related increases in the frequency of haemoglobin adducts in humans and dose related increases in the number of adducts in DNA and haemoglobin in exposed rodents;

iv) induces gene mutations and heritable translocations in germ cells in exposed rodents;

v) is a powerful mutagen and clastogen at all phylogenetic levels.

B.6.8.2 Adduct formation in experimental animals

a) The ethylene metabolite, ethylene oxide, reacts with nucleophilic centres in protein and DNA. The haemoglobin adducts N-(2-hydroxyethyl)histidine and N-(2-hydroxyethyl)valine have been used as internal dose monitors for the formation of ethylene oxide from ethylene. In male CBA mice, it has been reported that 7-8% of inhaled ethylene is metabolised to ethylene oxide. These mice were exposed to ethylene at concentrations below 23 mg/m^3 (20 ppm) at which first-order kinetics of metabolism can be assumed. The value is equal to the alveolar retention of ethylene at steady state and is similar to the values calculated for rats and humans. The levels of the haemoglobin-hydroxyethyl valine adduct was determined in Fischer rats and Syrian hamsters exposed for six months to gasoline and diesel exhausts. In hamsters, the levels of haemoglobin-hydroxyethyl valine adduct increased almost linearly with dose. At the highest dose, the levels were similar in male rats and hamsters and in

female rats and hamsters. The values were about 50-90% of those predicted from data on mice and indicated that ethylene behaves similarly in these species.

(Ehrenberg *et al*, 1977; Segerback, 1983/IARC 1994)

b) Ethylene oxide is present in cigarette smoke and smokers have higher haemoglobin adduct levels (average of 170 pmol/g of globin) than non-smokers (average of 20 pmol/g of globin). The adduct levels in non-smokers indicate widespread background exposures. Ethylene formed endogenously may contribute to this background. The highest adduct levels have been found in ethylene production workers (up to 16000 pmol/g of globin). Patients treated with cytostatic drugs that transfer hydroxyethyl groups also show elevated adduct levels (e.g. 330 pmol/g of globin for nimustine a chloroethyl nitroso urea derivative). Based on the hydroxyethyl valine adduct levels for smokers (10 cigarettes/day; 120 pmol/g of globin), non-smokers (50 pmol/g of globin) and steriliser operators (0.2-8.5 ppm; median value of 16.2 pmol/g of globin with a range of 5.2-32.7 pmol/g of globin) were reported.

(B-G-G 2003)

B.6.8.3 Human data (Ethylene exposure)

B.6.8.3.1 Volunteer studies (ADME)

a) The inhalation pharmacokinetics of ethylene was investigated in human volunteers at atmospheric concentrations of up to 50 ppm (0.1575 mg/l) by gas uptake in human volunteers in a closed spirometer system. The uptake, exhalation and metabolism, can be described by first-order kinetics. Uptake of ethylene into the body was low. Clearance due to uptake, which reflected the transfer rate of ethylene from the atmosphere into the body, was 25 litres per hour for a man of 70 kg. This value represented only 5.6% of the experimentally obtained alveolar ventilation rate of 150 litres per hour. The majority (94.4%) of ethylene inhaled into the lungs was exhaled again without becoming systemically available via the blood stream.

Maximal accumulation of ethylene in the same man, determined as the thermodynamic partition coefficient whole body:air was 0.53. The concentration ratio at steady state was even smaller (0.33), owing to metabolic elimination. Clearance due to metabolism, in relation to the concentration in the atmosphere, was calculated to be 9.3 litres per hour for a man of 70 kg. This indicates that at steady state about 36% of systematically available ethylene was eliminated metabolically and 64% was eliminated by exhalation as the unchanged substance, as could be calculated from the values of clearance of uptake and of clearance of metabolism. The biological half-life was 0.65 hr. The alveolar retention of ethylene at steady state was calculated to be 2-3%. From theoretical considerations of the lung uptake of gases and vapours, it could be deduced that the low uptake rate of ethylene was due to its low solubility in blood (Ostwald`s solubility coefficient for human blood at 37°C: 0.15). This summary stated that ethylene gives rise to minute levels of ethylene oxide and that the maximum conversion of ethylene to ethylene oxide in humans was estimated to be 4 %.

(Filser *et al*, 1992/OECD:SIDS)

B.6.8.3.2 Occupational exposure

a) Personal and stationary monitoring of ethylene in a company where this gas was used for controlling the ripening of bananas showed air concentrations to be in the range of 0.02-3.85 mg/m^3 (0.02-3.35 ppm) with an estimated average concentration of 0.35 mg/m^3 (0.3 ppm).

(Tornqvist *et al* , 1989a/IARC)

b) Exposure to fire-fighters during the 'knockdown' phase of a fire showed a concentration of 53 mg/m^3 (46 ppm) ethylene; none was detected during the 'overhaul, phase. In laboratory studies, ethylene has been detected as a thermal degradation product of polyethylene and polypropylene.

(Hoff *et al*, 1982; Jankovic *et al*, 1991/IARC)

c) In a preliminary study, the miscarriage rate (6/15 pregnancies) in Swedish workers in five local petrochemical plants was higher than 1549 woman from outside the industry. Ethylene was the main product in four 4/5 of the petrochemical plants. No data were provided on occupational levels but measurements made in areas surrounding the plants indicated that ethylene was present in concentrations up to 10-fold higher that the other main pollutants (propylene, ethane, propane and phenol).

(Axelsson and Molin, 1988/BIBRA Toxicity Profile 1993)

d) A brief abstract notes that there was a higher than expected rate of miscarriage and gynaecological disease among female operatives of a polyethylene plant who were exposed to ethylene concentrations in the range of about 40-60 ppm and high levels of noise.

(Yakubova *et al*, 1976/BIBRA Toxicity Profile 1993)

B.6.8.3.3 Environmental exposure

a) Ethylene concentrations in ambient air and remote rural sites worldwide are generally in the range of <1-5 µg/m^3. In urban and indoor air contaminated with combustion products, ethylene concentrations range up to 1000 µg/m^3.

(Seinfeld, 1989; Colbeck & Harrison, 1985; Sawada & Totsuka, 1986/IARC)

b) Vehicle exhaust emissions make a significant contribution to urban air concentrations of ethylene. Several authors have monitored traffic emissions which ranged from 93-212 mg/km and 9.8-405 5 µg/m^3 depending on the site sampled (e.g. urban intersection or tunnel).

(Bailey *et al*, 1990a & b; Barrefors & Petersson, 1992/IARC)

c) Smoking is also a significant source of exposure to ethylene (1-2 mg ethylene are released per cigarette). The exposure of the average smoker is roughly 10 times that from urban air pollution. In two studies, the ethylene levels in tavern air were 56 and 110 µg/m^3 while the corresponding outdoor air concentrations at the time were 16 and 12 µg/m^3.

(Person *et al*, 1988; Lofroth *et al*, 1989/IARC)

d) Plants that normally produce ethylene at 0.6-6 µg/kg fresh weight per hour may produce up to 120 µg/kg per hour during ripening of fruits and during senescence and loss of leaves.

(Dorffling, 1982; Tille *et al* 1985/IARC).

B.6.8.3.4 Endogenous formation

Endogenous production of ethylene can be deduced from its exhalation by unexposed subjects. For a man of 70 kg, a mean production rate of 32 nmol/hour (0.9 µg/hour) and a corresponding mean body burden of 0.011 nl/ml tissue [equivalent to 0.44 nmol/kg bw or 0.012 µg/kg bw] was calculated for ethylene gas. The amount of ethylene in the breath of women is increased significantly at the time of ovulation. No difference was observed in the basal ethylene outputs of non-pregnant and pregnant women and of men.

(Filser *et al*, 1992; Harrison, 1981/IARC)

B.6.8.3.5 Adduct formation

a) The haemoglobin adducts N-(2-hydroxyethyl)histidine and N-(2-hydroxyethyl)valine have been used as internal dose monitors for the formation of ethylene oxide from ethylene in humans. Higher levels of adducts were found in cigarette smokers than in non-smokers and ethylene and ethylene oxide were considered to be major causes of the elevated adduct levels.

(Tornqvist *et al*, 1986b & 1989a/IARC 1994)

b) Non-smoking fruit store workers exposed occupationally to atmospheric ethylene at 0.023-3.85 mg/m^3 (0.02-3.35 ppm) while ripening bananas had levels of 22-65 pmol/g haemoglobin-(hydroxyethyl valine) whereas non-smoking controls had 12-27 pmol/g haemoglobin-(hydroxyethyl valine). On the basis of a mean exposure concentration of 0.345 mg/m^3 (0.3 ppm), it was estimated that about 3% (range 1-10%) of inhaled ethylene as metabolized to ethylene oxide. This percentage is in agreement with the alveolar retention at steady state calculated from pharmacokenitics. An increment of 100-120 pmol/g haemoglobin-(hydroxyethyl valine) was estimated for a time-weighted average exposure (40 hours/week) to 1.15 mg/m^3 (1 ppm) ethylene. On the basis of the relationship between haemoglobin-(hydroxyethyl valine) levels and exposure levels of ethylene and ethylene oxide, the amount of ethylene metabolised to ethylene oxide can be calculated; 1 mg ethylene/kg bw is equivalent to a tissue dose of ethylene oxide of 0.7 x 10^{-6} mol x h/l (0.03 mg x h/kg bw). This value is in agreement with the value of 0.5 x 10^{-6} mol x h/l that can be calculated from the pharmacokinetic data for ethylene and ethylene oxide published by Filser *et al*, 1992.

(Tornqvist *et al*, 1988 & 1989a; Kautiainen & Tornqvist, 1991; Filser *et al*, 1992/IARC 1994)

c) The following tabulated exposure data was presented in an article reviewing the current position with respect to some biomarkers and volatile organic chemicals (mainly 1,3-butadiene).

Table B.6.5 Haemoglobin adduct levels (N-terminal hydroxyethyl valine) in smokers and non-smokers and in subjects with occupational exposure.

[a]Controls	Exposure groups		
	Type of exposure	Exposure concentration	Adduct level (average, range)
Ethylene (pmol/g globulin)			
[b]Non-smokers 20 (12-27)	Occupational	0.3 (0.1-1) ppm	43 (22-65)
Non-smokers 16.1 ± 2.1	Tobacco smoking	1-25 cigarettes/day	146 (50-335)
Non smokers 63 ± 2.1	Tobacco smoking	>15 cigarettes/day	Maternal blood 361 ± 105
Newborn babies blood 42 ± 18			New born babies blood) 147 ± 105
Ethylene oxide (pmol/g globulin)			
14-26	Occupational	Low: 28 ppm/week	84-2070

Key a) Background levels (average, range or mean ± SD). b) See B.6.8.3.5 b above.

The accumulation of stable haemoglobin adducts during prolonged exposure is the result of daily increments to the adduct level and daily losses due to the removal of the oldest fraction of the erythrocytes from the circulation. After exposure for a period of time exceeding 126 days in humans, a steady-state adduct level is attained. Thus, the measurement of stable adducts gives information on exposure during the months before blood sampling. Tates *et al* (1995) studied hydroxyethylvaline adducts in haemoglobin of four workers accidentally exposed to high concentrations of ethylene oxide. The adduct levels decreased linearly over time and reached background levels after approximately 110 days. Contrary to protein adducts, DNA adducts are subjected to repair and their stability varies considerably between cell type. In the absence of information on adduct stability, DNA adduct measurements give only qualitative information on exposure.

(http://www.ehponline.org/members/1996/Suppl-5/osterman-golkar-full.html)

~~**B.6.8.3.6 Residue data for ethylene and its metabolites in potatoes**~~

~~a) Endogenous concentrations of ethylene range between 0.0007-0.15 ppm for non-sprouting potato tubers and 0.1-3ppm for sprouted tubers. It was also stated that ethylene and its potential metabolites were not identified in treated potatoes at levels exceeding those found in control potatoes. Residue data for potatoes treated with 4 ppm ethylene for 150 days of storage. The residues, chloroethanol, dichloroethane, bromoethanol, ethylene oxide and ethylene glycol (including its glucoside) residues were in total less than 0.1 ppm. Residues of ethylene oxide were stated to be <2 ppm (the lower limit of quantitation of the analytical method employed). In addition, the processing or cooking of tubers is expected to result in a reduction of volatile residues (e.g. ethylene oxide) by up to 90% (no actual data included in the report).~~

~~(HC 2001)~~

b) The internal levels of dissolved and absorbed ethylene in Anjou pears during ripening have been determined. No exogenous ethylene was applied in order to establish the endogenous level in the natural ripening process. In pears, the reported internal ethylene concentrations ranged from 0.02-44.66 µl/l.

(Wang and Mellenthin, 1972)

B.6.9 Medical data and information (IIA 5.9)

The following medical data and information for ethylene was provided. The data/information in this section has not been assessed by the RMS.

B.6.9.1 Medical surveillance of manufacturing plant personnel (AII 5.9.1)

Personal and stationary monitoring of ethylene in a company where ethylene was used for controlling the ripening of bananas showed air concentrations to be in the range of 0.02 - 3.35 ppm (0.02 - 3.85mg/m^3). In a study on exposure of firefighters, samples taken during the "knockdown" phase of a fire showed a concentration of 46 ppm (53 mg/m^3) ethylene. A study was carried out among workers at a Swedish petrochemical plant in order to assess the amounts and effects of ethylene exposure. The study was carried out in two parts, part one in 1989 and part two in 1993. Eight workers exposed to high levels of ethylene (4 mg/m^3) and 3 workers exposed to lower levels (0.1 - 0.3 mg/m^3) were compared to nine controls exposed to 0.01 mg/m^3. All exposed workers showed elevated levels of haemoglobin adducts and adduct formation was dose-related. The results indicated that about 1% of the inhaled ethylene was metabolized to ethylene oxide. Part two of the study, which included four workers, was designed to more accurately determine exposure level, which had a mean of 4.5 mg/m^3. The results confirmed part one, showing that about 1% of inhaled ethylene was metabolised to ethylene oxide and the maximum fraction to be converted was estimated to be 4%.

There have been two preliminary but independent reports of increased miscarriage rates among women working in the petrochemical industry. Elevated ethylene concentrations were mentioned as a possible reason, but this has not been confirmed. No firm conclusions can be drawn from these reports. A preliminary study found no increase in lung cancer incidence in 31 workers exposed to ethylene (at unspecified levels) at a US petrochemical factory. However, due to the limited number of exposed workers in this study no conclusions regarding ethylene not causing cancer can be

drawn. A study of workers at an US petrochemical plant found that an increased risk of developing brain cancer was associated with exposure to (unspecified levels of) a number of chemicals including ethylene. However, the investigators were unconvinced that the association reflected a causal relationship (OECD SIDS).

According to Toxnet (Databases in toxicology and environmental health) HSDB, 2003, it is estimated that 12,280 workers are potentially exposed to ethylene in the U.S.A.

B.6.9.2 Clinical cases and poisoning incidents (IIA 5.9.2)

Symptoms: dizziness, headache, nausea, and loss of co-coordination.

The following are clinical effects of acute exposure to ethylene, reported in the OECD SIDS assessment profile for ethylene:

ACUTE EXPOSURE: Simple asphyxiants displace oxygen from the breathing atmosphere primarily in enclosed spaces and result in hypoxia. Four stages are described, depending on the arterial oxygen saturation:

1) INDIFFERENT STAGE (% O_2 Saturation: 90%):

Night vision: decreased

2) COMPENSATORY STAGE (% O_2 Saturation: 82 to 90%)

1 Respiratory rate: compensatory increase
2. Pulse: compensatory increase
3. Night vision: decreased further
4. Performance ability: somewhat reduced
5. Alertness: somewhat reduced

Symptoms may begin in those with significant pre-existing cardiac, pulmonary, or haematological diseases

3) DISTURBANCE STAGE (% O_2 Saturation: 64 to 82%)

1. Compensatory mechanisms become inadequate
2. Air hunger
3. Fatigue
4. Tunnel Vision
5. Dizziness
6. Headache
7. Belligerence
8. Euphoria
9. Visual acuity: reduced
10. Numbness and tingling of extremities
11. Hyperventilation
12. Poor judgement
13. Memory loss
14. Cyanosis

Decreased ability for escape from toxic environment

4) CRITICAL STAGE (%O_2 Saturation: 60 to 70% or less):

1. Deterioration in judgement and coordination may occur in 3 to 5 minutes or less
2. Total incapacitation and unconsciousness follow rapidly

- All early effects may decrease ability for self-rescue from the toxic environment.
- Some agents causing asphyxia are stored and transported in compressed or liquid form and can cause frostbite on direct skin contact.

CARDIOVASCULAR EFFECTS

1) An increased pulse rate may occur.
2) Cardiac manifestations of prolonged or severe hypoxia may include atrial or ventricular dysrhythmias, hypotension, myocardial ischemia, myocardial infarction, and eventual aystole.
3) "Sudden sniffing death", or cardiac arrest, is reported following intentional inhalation of hydrocarbons.

RESPIRATORY EFFECTS

1) Hyperventilation may develop.
2) Cyanosis may occur.
3) Bronchoconstriction and respiratory depression may be seen.
4) Pulmonary oedema and lung congestion may occur.

NEUROLOGIC EFFECTS

1) Various disturbances including headache, dizziness, mood disturbances, numbness of the extremities, sleepiness, mental confusion, poor judgement and coordination, and memory loss may occur.
2) Prolonged or severe hypoxia results in unconsciousness.
3) Prolonged asphyxia may produce CNS injury.
4) Hemiparesis has been reported with volatile substance abuse.
5) Cerebral oedema with brainstem herniation may occur.
6) Seizures have been reported following intentional inhalation.

GASTROINTESTINAL EFFECTS: Nausea, vomiting, and gastrointestinal haemorrhage may develop

MUSCULOSKELETAL EFFECTS: Rhabdomyolysis and seizures have been reported.

REPRODUCTIVE HAZARDS**:** Possible consequence of oxygen deprivation in the unborn is controversial. Cerebral palsy, previously thought to be due to acute hypoxia during labour and/or childbirth, remains poorly understood.

There are also some acute hazard of dermal and ocular frost burns. Toxnet (Databases in toxicology and environmental health) HSDB, 2003, states that acute dermal exposure may cause frostbite injury. Severe tissue burns have been reported

B.6.9.3 Exposure of the general population and epidemiological studies (IIA 5.9.3)

Ethylene is ubiquitous in the environment, arising from both natural and man made sources. Major natural sources are emissions from vegetation of all types, where it functions as a plant hormone. The main anthropogenic sources are combustion of gas, fuel, coal and biomass. The highest exposure to humans is due to ethylene from car motors. Ethylene had been in general use as an anaesthetic for many years. It has been replaced by more modern anaesthetics, mostly due to the high explosion risk. Today, elevated exposure of humans is limited to a low number of workers at ethylene protection plants, and these involved in transport of ethylene. The total global emission has been estimated to be 18-45 x 10^6 t/y, of which approximately 74% is released from natural sources and 26% from anthropogenic sources. Emission from fuel oil combustion is equal to approximately 4% of total global emissions (OECD SIDS).

In an epidemiological study, following exposure to ethylene, no increase in risk of developing myelomas was noted.

B.6.9.4 Clinical signs, symptoms of poisoning and details of clinical tests (IIA 5.9.4)

Symptoms included dizziness, headache, nausea, and loss of co-coordination. Please refer to sections B.6.9.2 and B.6.9.3.

B.6.9.5 First aid measures (IIA 5.9.5)

Move the victim to fresh air and call the medical emergencies services. Give artificial respiration if the victim is not breathing or administer oxygen if breathing is difficult. Remove and isolate contaminated clothing and shoes. In case of contact with liquefied gas, thaw frosted parts with lukewarm water. In case of burns, immediately cool affected skin for as long as possible with cold water. Do not remove clothing if adhering to the skin. Keep the victim warm and quiet. Ensure that medical personnel are aware of the material involved and take precautions to protect themselves (US Department of Transport, 2004).

Inhalation: Move to fresh air. If not breathing, give artificial respiration. If breathing is difficult, give oxygen. Get medical attention immediately.

Skin Contact: Wash affected area extremely thoroughly with soap and water. Seek medical attention if irritation persists. Remove all contaminated clothing.

Eye Contact: Rinse immediately with copious amounts of tepid water for at least 15 minutes and obtain medical aid.

Ingestion: Not applicable Ethylene is a gas at normal temperature and pressure.

B.6.9.6 Expected effects and duration of poisoning as a function of the type, level and duration of exposure or ingestion (IIA 5.9.6)

Under environmental conditions, ethylene is a gas; therefore the most probable route of human exposure is via inhalation. There is no evidence to suggest ethylene is an eye or skin irritant.

Concentrations of less than 20% ethylene in air (25000 ppm) do not cause harmful effects and are not irritating to the nose, throat or lungs. High concentrations of ethylene can displace oxygen in air and cause life-threatening asphyxiation. When ethylene is used as a compressed gas, high concentrations can be generated quickly if a leak occurs.

The normal oxygen concentration in air is 20.9%. At 15-16% oxygen, symptoms of sleepiness, fatigue, loss of concentration, errors in judgement and confusion are masked by a state of euphoria, giving a false sense of security and well-being. An oxygen concentration of 12% or lower can cause unconsciousness quickly and without warning. In some cases disturbed respiration, abnormal fatigue. Emotional upsets, nausea, vomiting and inability to move freely may occur. Concentrations below 6% can result in respiratory collapse and death. If the victim survives, some or all organs, including the central nervous system and brain, may show damage due to oxygen deprivation.

Marked memory disturbances have also been reported following exposure to 37.5% (37500 ppm) of ethylene for 15 minutes (this effect may have been due to oxygen deprivation) (CCOHS, 2000).

Animal toxicity information suggests that ethylene will not cause significant health effects following long-term exposure.

B.6.10 Summary of mammalian toxicology and proposed ADI, AOEL, ARfD and MAC (drinking water limit) (IIA 5.10)

No oral ADME studies have been submitted or cited; the available data has been generated using inhalation exposure. A metabolic pathway has not been proposed for ethylene in mammals.

Following inhalation of radiolabelled parent, absorption appeared to be rapid (within minutes) but the systemic uptake from the lungs was low. It has been estimated that approximately 83% of the ethylene that reaches the lungs is exhaled unchanged while 17% is absorbed. Distribution is widespread throughout the body. In rats, about 24-29% of systemically available ethylene is eliminated by metabolism and the remainder by exhalation of the unchanged substance. Elimination appears to be rapid. Most of the inhaled ethylene was exhaled unchanged with smaller amounts excreted in urine and faeces and as exhaled carbon dioxide. Apart from ethylene oxide and its metabolites [and the urinary metabolite 5-(2-hydroxyethyl)cysteine in mice], there appears to be little or no information or investigations into other potential metabolites of ethylene.

Ethylene is not classifiable via the acute inhalation route according to EC criteria (based on cited data). There are insufficient data to classify ethylene via the acute oral and dermal routes or for skin and eye irritancy and skin sensitisation using the normal EC criteria. However, based on industrial use and its use as an anaesthetic,

ethylene gas dose not appear to be classifiable as a skin or eye irritant or a skin sensitiser. It should be noted that liquefied or pressurized ethylene gas can cause frostbite damage.

No data were submitted for the oral or dermal routes for short-term exposure (or cited from the published literature). The available short term repeat dose inhalation studies reported effects on blood parameters and the nervous system. A 90-day study did not report any effects at dose levels up to 11.5 mg/l of air, the highest dose tested (this study may have been conducted by IBT under contract to the CIIT (see comments on carcinogenicity study).

There was no evidence genotoxicity in the *in vitro* bacterial and chromosome aberration assays or the *in vivo* the bone marrow micronucleus assays in rats or mice.

No long-term studies were submitted for the oral route of exposure (or data cited from the published literature). Summaries of a single long-term rat inhalation study are available in the literature. Generally, the authors of these summaries have concluded that there no evidence of chronic toxicity in this study and no evidence of compound-induced carcinogenicity. However, some authors have expressed doubts over the quality and reporting of the study (conducted by the discredited contract laboratory IBT), the interpretation of the findings in this study (e.g. mononuclear cell leukaemia) and their relationship to the toxicological effects induced by the metabolite ethylene oxide. The background to IBT can be found at section 3.1.8 of http://www.oecd.org/dataoecd/13/15/36045203.pdf]. IARC (1994) concluded that the evidence of carcinogenicity in experimental animals and humans was inadequate, however, several workers have stated that the possible carcinogenic risk from inhaling ethylene should be reconsidered/re-evaluated based on the potential exposure to ethylene (very high tonnage), the limited database and the metabolism of ethylene to ethylene oxide.

The available reproduction data are limited and the quality is equivocal. A reproductive screen test concluded there was no compound induced parental or foetal toxicity or developmental toxicity over a single generation (i.e. up to 4 days post partum) at concentrations up to 5.75 mg/l or 5000 ppm (approximately equivalent to a systemic exposure of 0.575 mg/l or 500 ppm). However, some published data (of unknown quality) appears to indicate that post-natal development could be adversely affected at a dose level of 2.62 ppm.

No specific neurotoxicity studies have been submitted for evaluation but there are some indications of treatment-related effects on the nervous system.

Ethylene is metabolised to ethylene oxide in experimental animals. Two metabolic pathways have been identified in experimental animals and humans, the hydrolysis of ethylene oxide to 1,2-ethanediol and conjugation with glutathione to produce S-(2-hydroxyethyl)cysteine and N-acetyl- S-(2-hydroxyethyl)cysteine (Fig B.6.3). Since ethylene oxide can react with chloride ions, and this reaction is acid catalysed, 2-chloroethanol might be expected to be a metabolite, especially after oral administration.

Ethylene oxide is currently classified by the ECB as a Cat: 2 for carcinogenicity (R45) and Cat: 2 for mutagenicity (R46). In addition, the literature indicates that ethylene oxide induces reproductive effects in experimental animals (foetal toxicity in the presence and absence of maternal toxicity, teratogenicity in mice, sperm effects) and there is some limited evidence of spontaneous abortions in humans. Ethylene oxide has also been associated with neurotoxicity and cataracts in the ocular lens. It is also currently classified by the ECB as Toxic by inhalation (R23) and as an irritant (R36/37/38) and the literature also indicates that it can also induce sensitisation responses. Chloroethanol, a possible reaction product with chloride in food, is also currently classified by the ECB as a Cat:2 carcinogen.

Ethylene oxide is an electrophilic agent that alkylates nucleophilic groups in biological macromolecules, i.e. including DNA and protein (e.g. haemoglobin & albumin). It is considered likely that the toxicological effects of ethylene oxide arise primarily from the direct alkylation of macromolecules. Since ethylene oxide is formed during the metabolism of ethylene (a natural body constituent) both endogenous and exogenous sources of ethylene and ethylene oxide will contribute to the background alkylation of macromolecules. There is extensive evidence of genotoxicity (*in vitro* and *in vivo* effects) and carcinogenicity indicating that ethylene oxide is a potent genotoxic carcinogen in experimental animals (via oral and inhalation routes).

Endogenous, environmental and man-made sources of ethylene exposure are well documented in the literature. Ethylene is a natural product of many plants and it is released into the atmosphere at various stages of their life cycle. Other major sources contributing to background levels of ethylene are industrial and volcanic emissions, natural gas, the burning of vegetation, smoking cigarettes, the combustion of fossil fuels (including vehicle exhaust emissions) and in food materials. Endogenous but unidentified sources of ethylene exist in man and experimental animals.

Although ethylene is classified as a "simple asphyxiant" and results in asphyxia due to oxygen displacement in enclosed spaces, the extensive list of adverse effects in humans (B.6.9) indicates that this is an oversimplification and requires further consideration. Ethylene is metabolised to ethylene oxide, a known genotoxic carcinogen, and forms adducts with DNA, haemoglobin and other proteins. The U.S. Department of Labor (Occupational Safety & Health Administration) web site states that the health effects of long-term or repeated exposure to ethylene are not known (www.osha.gov). Occupational exposure has been associated with an increased incidence of reproductive effects and brain tumours in workers in the petrochemical industry but the quality of these epidemiological studies was questioned and it was concluded that there was no convincing evidence of any causal links. However, non-smoking fruit store workers exposed occupationally to atmospheric ethylene had higher levels of haemoglobin adducts compared to non-smoking controls.

No specific occupation exposure limits have been recommended in the UK or in most developed countries but Switzerland has established a time-weighted average occupational limit of 11500 mg/m^3 (OECD: SIDS). In Germany, no exposure limit is given for ethylene because it is 'justifiably suspected of having carcinogenic potential' (Deutsche Forschungsgemeinschaft, 1993/IARC 1994).

B.6.10.1 Acceptable Daily Intake (ADI)

Although ethylene is an important industrial chemical, there appears to be only a limited number of standard toxicity studies and human epidemiology studies in the public domain. No oral toxicity studies are available for ethylene. The majority of the available data have been generated using inhalation exposure and the various international regulatory authorities appear to have relied upon the 2-year rat inhalation study to conclude that ethylene is not a carcinogen. In addition, the cited regulatory authorities have relied upon metabolism data generated from acute/short-term inhalation studies to estimate the predicted conversion of ethylene to ethylene oxide.

Since there are insufficient data to set an ADI for ethylene, any approvals for the use of ethylene as a growth regulator used to ripen bananas must be dependant on the residue levels of ethylene and its metabolites after treatment being no greater than the normal background rates in potatoes and bananas~~. The Health Canada (2001) document states that analytical data for ethylene and its potential metabolites in ethylene treated potatoes were either non-detectable or were at similar levels to any measurable residues found in controls (no actual exposure levels or analytical results were included in the document).~~

No analytical data was submitted for ethylene treated bananas which would substantiate that the residue levels were equal to or similar to untreated bananas. Without these relevant residue data, it is not possible to conclude that the use of ethylene for the requested uses would not present an unacceptable risk to human health.

As indicated by the Health Protection Branch of Health Canada in the "Health and Safety Status Report" for ethylene (May 1994), an acceptable daily intake (ADI) is not required for ethylene, since it is a naturally occurring chemical produced by fruits and vegetables, including potatoes, during senescence. Ethylene is also a naturally occurring endogenous chemical in humans and laboratory animals and has been identified in the air exhaled by unexposed rats and humans. Potential ethylene metabolites have also been shown to occur naturally. Analytical data for these metabolites in treated potatoes showed that residue levels were either non-detectable or were at levels similar to any measurable residues found in controls (Health Canada, 2001).

B.6.10.2 Acute Reference Dose (ARfD)

There are insufficient data to set an ARfD. Apart from the formation of adducts, there are no clear obvious effects of acute exposure presented in the literature and the relevant data for oral exposure is sparse or non-existent. Approval is therefore dependant on the residue levels of ethylene and its metabolites after treatment being no greater than the normal background rates in bananas.

The following was proposed:

An acute reference dose (ARfD) was not established, since ethylene was considered unlikely to present an acute hazard. The available literature suggests that there are no significant treatment-related findings to indicate a concern in acute dietary risk

assessment. The potential risks to humans from exposure to ethylene are considered negligible due to low toxicity concerns and the widespread use of ethylene as an anaesthetic with little concomitant toxicity (Health Canada, 2001).

B.6.10.3 Admissible Operator Exposure Level (AOEL)

There is insufficient data to set an AOEL. However, the current occupational exposure levels and application methods suggest that the use of ethylene is acceptable. However due to some reports of increased levels of haemoglobin adducts in fruit plant workers, it is recommended that exposures be kept as low as reasonably achievable e.g. use of RPE or engineering controls.

B.6.10.4 Maximum Allowable Concentration (MAC: drinking water limit)

There are insufficient data to set a health based limit. The EU limit for the concentration of any pesticide in drinking water is 0.1 μg/l.

B.6.10.5 Classification and labelling

B.6.10.5.1 Ethylene

a) Current ECB classification

R67	Vapours may cause drowsiness and dizziness.
S2	Keep out of the reach of children
S46	If swallowed, seek medical advice immediately and show this container or label.

b) Proposed classification

Ethylene is converted into ethylene oxide in rats (5-10%) and humans (estimated values of <4%). The data base is inadequate to conclude a robust proposal for the classification of ethylene for carcinogenicity and reproductive toxicity. However, assuming that humans metabolise ethylene to ethylene oxide, in the absence of data on ethylene, the classification could take account of the potential ethylene oxide exposure.

c) Classification of liquefied or pressurised ethylene

Liquefied or pressurized ethylene gas can cause frostbite damage (this may trigger part of the risk phrase RSh Directive 2003/82/EC).

B.6.10.5.2 Ethylene oxide

Current ECB classification

CAT: 2 carcinogenicity & CAT: 2 mutagenicity

R23	Toxic by inhalation
R36/37/38	Irritating to eyes, respiratory system and skin
R45	May cause cancer
R46	May cause heritable genetic damage
S45	If swallowed or if you feel unwell, seek medical advice immediately (show the label where possible).
S53	Avoid exposure-Obtain special instructions before use.

B.6.10.5.3 1,2-ethanediol (ethylene glycol)

Current ECB classification

R22	Harmful if swallowed
S2	Keep out of reach of children

B.6.10.5.4 1,2-dichloroethane (ethylene dichloride)

Current ECB classification

CAT: 2 carcinogenicity

R22	Harmful if swallowed
R36/37/38	Irritating to eyes, respiratory system and skin
R45	May cause cancer
S45	In the case of accidents or if you feel unwell seek medical advice immediately (show the label where possible).
S53	Avoid exposure-Obtain special instructions before use.

B.6.11a Acute toxicity, irritancy and skin sensitisation of the 'Ethylene' (IIIA 7.1)

'Ethylene' in cylinders contains 60 g/kg ethylene (99.9% purity) and 940 g/kg nitrogen. A single source is used by all five notifiers (i.e. Air Liquide, Air Products, Coleacp, Linde Ag and Praxair).

B.6.11.1a Acute oral toxicity in rats (AIII 7.1.1)

No studies submitted.

B.6.11.2a Acute dermal toxicity (AIII 7.1.2)

No studies submitted.

B.6 11.3 Acute inhalation toxicity (AIII 7.1.3)

No studies submitted.

B.6.11.4a Skin irritancy (AIII 7.1.4)

No studies submitted

B.6.11.5a Eye irritancy (AIII 7.1.5)

No studies submitted.

B.6.11.6a Skin sensitisation (AIII 7.1.6)

No studies submitted.

B.6.11.7a Summary of the toxicity of ethylene

Apart from the dangers of asphyxiation in confined spaces and potential frost bite injury, the potential acute toxicity, irritation and skin sensitisation effects of this product are likely to be limited to those induced by ethylene gas.

B.6.11.8a Toxicological data on non active substances (IIIA 7.4)

The nitrogen may cause asphyxiation at high concentrations in enclosed spaces due to oxygen deficiency. The symptoms of oxygen deficiency include respiratory difficulty, ringing in ears, headaches, shortness of breath, wheezing, headache, dizziness, indigestion, nausea, and at high concentrations, unconsciousness or death may occur.

B.6.11.9a Proposal for classification and labelling

Apart for the observation that liquefied or pressurized ethylene gas can cause frostbite damage (this may trigger part of the risk phrase RSh Directive 2003/82/EC), no classification is proposed for the acute toxicity, irritation or skin sensitisation of 'Ethylene' (a mixture of ethylene and nitrogen).

B.6.12a Dermal absorption studies (IIIA 7.3)

Not applicable.

B.6.13a Toxicological data on non active substances (IIIA 7.4)

There are no hazard warnings on the MSDS that give rise to toxicological concerns with respect to the classification of 'Ethylene Gas' (a mixture of ethylene and nitrogen).

B.6.11b Acute toxicity, irritancy and skin sensitisation of 'Restrain Generator Fuel' (IIIA 7.1)

The notifier of 'Restrain Generator Fuel' states that it contains 96% ethanol (i.e. food grade ethanol without any denaturant); the product is used to generate ethylene using a catalytic generator.

B.6.11.1b Acute oral toxicity in rats (AIII 7.1.1)

No studies submitted.

B.6.11.2b Acute dermal toxicity (AIII 7.1.2)

No studies submitted.

B.6 11.3b Acute inhalation toxicity (AIII 7.1.3)

No studies submitted.

B.6.11.4b Skin irritancy (AIII 7.1.4)

No studies submitted.

B.6.11.5b Eye irritancy (AIII 7.1.5)

No studies submitted.

B.6.11.6b Skin sensitisation (AIII 7.1.6)

No studies submitted.

B.6.11.7b Summary of the toxicity of 'Restrain Generator Fuel'

The acute toxicity, irritation and skin sensitisation effects of 'Restrain Generator Fuel' are driven by the ethanol content of the product. For a full evaluation of ethanol, please refer to the Ethanol Draft Assessment Report.

Ethanol is considered to be of low toxicity via the acute oral, dermal and inhalational routes. It is not a skin irritant or a skin sensitiser but there is some evidence that ethanol is an eye irritant and a respiratory irritant. Therefore, 'Restrain Generator Fuel' is classifiable as an eye irritant and a respiratory irritant based on the ethanol content.

B.6.11.8b Toxicological data on non active substances (IIIA 7.4)

The available data and information on denatured ethanol do not give rise to toxicological concerns with respect to the classification of 'Restrain Generator Fuel'.

B.6.11.9b Proposal for classification and labelling

Based on the ethanol content, 'Restrain Generator Fuel' is classifiable as given below in subsection (a). This level of classification for the carcinogenicity, mutagenicity and reproductive toxicity of ethanol is supported by publicly available animal and human data. Further discussion is presented in the Ethanol Draft Assessment Report. The current ECB classification is presented below in subsection (b).

a) Classification currently being considered by the ECB

Hazard symbol(s) T

Indication of danger: Toxic

Risk phrases:

R36/37	Irritating to eyes and respiratory system.
R45 (CAT 1or 2: Carcinogen)	May cause cancer
R46 (CAT 2: Mutagen)	May cause heritable damage
R60 (CAT 1: Reproductive toxin)	May impair fertility
R61 (CAT 1: Reproductive toxin)	May cause harm to the unborn child
R64 (CAT 1: Reproductive toxin)	May cause harm to breast-fed babies

Safety phrases:

S2: Keep out of the reach of children.
S53: Avoid exposure-Obtain special instructions before use.
S45: In case of accident or if you feel unwell seek medical advice immediately (show the label where possible).

b) Current ECB classification of ethanol

According to the ECB web site, ethanol is currently unclassified for health effects

Note: The RMS is aware that the International Agency for Research on Cancer (IARC) is currently preparing an up-dated monograph on the carcinogenic effects of alcohol which is expected to be published in the near future.

B.6.12b Dermal absorption studies (IIIA 7.3)

In the absence of data, a dermal absorption value of 100% is proposed for the operator exposure calculations.

B.6.13b Toxicological data on non active substances (IIIA 7.4)

The notifier of 'Restrain Generator Fuel' states that this product contains 96% ethanol (i.e. food grade alcohol without a denaturant); therefore, any other minor constituents are unlikely to give rise to toxicological concerns with respect to classification.

B.6.14 Exposure data (IIIA 7.2)

Ethylene

The supported use of ethylene is as a plant growth regulator, intended for use in degreening and ripening of bananas. It is applied via compressed gas cylinders containing ethylene and nitrogen or by a catalytic generator. This produces ethylene by converting liquid fuel (ethanol) to ethylene gas and water vapour. Ethylene is applied in hermetic ripening rooms. The target concentrations for the two methods of generation are sufficiently similar to allow the major conclusions drawn vis-à-vis the scenario involving ethylene introduced from gas cylinders to apply to ethylene produced from ethanol. Exposure to ethanol from handling the product and preparing the generator equipment is considered in the Draft Assessment Report for ethanol.

	Target concentration	Source of information
Cylinders (ethylene gas)	600 – 1000 ppm	GAP table
Generator (ethanol)	4 – 1200 ppm	Label for 'Ethygen II'

Table 6.14.1 – Comparison of target concentrations achieved with two forms of ethylene generation

Ethylene is not classifiable via the acute inhalation route according to EC criteria (based on cited data). There are insufficient data to classify ethylene via the acute oral and dermal routes or for skin and eye irritancy and skin sensitisation using the normal EC criteria. However, based on industrial use and its use as an anaesthetic, ethylene gas dose not appear to be classifiable as a skin or eye irritant or a skin sensitiser. Liquefied or pressurized ethylene gas can cause frostbite damage (B.6.10).

There is insufficient data available to set an AOEL for ethylene (B.6.10.3).

Ethylene oxide

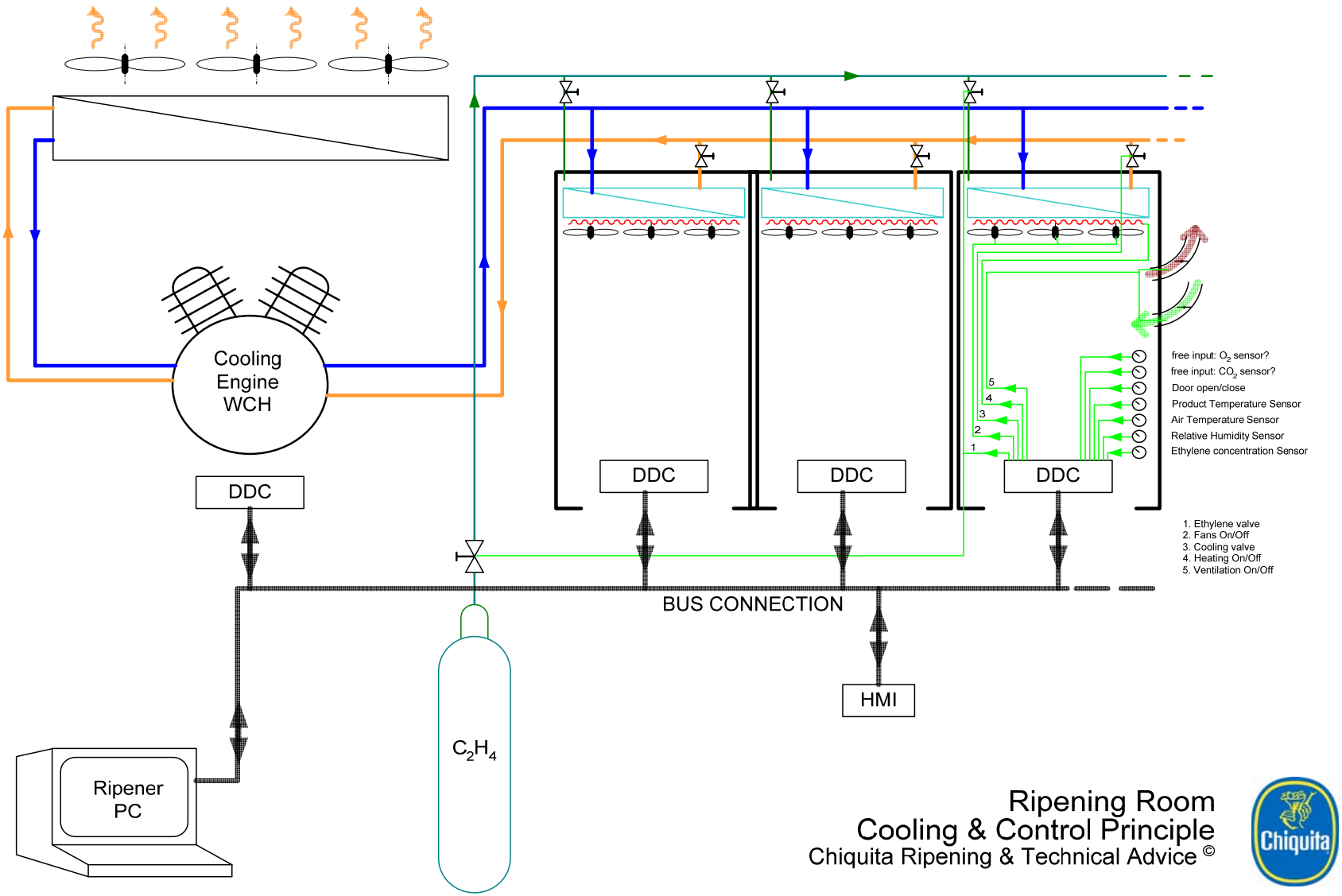
Ethylene oxide has been identified as a metabolite of ethylene (B.6.13). Ethylene is converted into ethylene oxide in rats (5-10%) and humans (estimated values of <4%) This metabolite is of toxicological concern and is therefore considered as part of this exposure assessment.

Ethylene oxide is currently classified by the ECB as a Cat: 2 for carcinogenicity (R45) and Cat: 2 for mutagenicity (R46). It is also currently classified by the ECB as Toxic by inhalation (R23) and as an irritant (R36/37/38) and the literature also indicates that it can also induce sensitisation responses.

Supported use

A summary of the treatment process is given below ;

Fig. 6.14.1.1 – A typical banana ripening installation



The gas is released from a number of cylinders and flow controlled by solenoid valves, one in the supply line after the cylinders and one in the line leading into each room in the store.

Fig. 6.14.1.2 – Ethylene station and cylinders

Fig. 6.14.1.3 Secondary solenoid valve controlling entry to a store room

(Note the cut-off valve which can be used if the secondary solenoid valve is broken.)

The valves are opened by direct digital controllers (DDCs). As the default position of both primary and secondary valves is 'closed' it is unlikely that ethylene will be accidentally released. Equipment is also incorporated which reduces the gas pressure from 200 bar in the supply tanks to 5 bar in the pipes and will alert the operator when the ethylene mixture is depleted.

The concentration of ethylene in the application room is monitored continuously and remotely by trained operators, to ensure the concentration remains near the target level throughout the application period. Typically, these are fully automated (computer controlled) systems which include automated door-locking mechanisms, which do not allow the doors to be opened when the treatment process is ongoing. Consequently, persons will not be present during the treatment process.

B.6.14.1 Operator exposure (IIIA 7.2.1)

Potential occupational exposure to ethylene may occur when entering the application room or its ventilation ductwork (e.g., for repair) after application of ethylene or when standing near the ventilation exhaust. This exposure scenario is considered under Worker exposure (B.6.14.3).

It is also possible that exposure could occur when handling the cylinders, for instance during changeover. The primary route of exposure would be via inhalation. Potential exposure to high concentrations of ethylene may occur in the event of a leak into an enclosed space. The proposed label includes precautionary statements regarding proper handling of the cylinders and gas release system to avoid leaks. Respiratory protection for entry into an area of unknown ethylene concentration is recommended on the draft label.

Although the primary route of exposure would be through inhalation, liquefied or pressurized ethylene gas can cause frostbite damage. In industry, however, PPE is normally worn to mitigate the risk of physical injury which could be caused by the heavy cylinders; gloves and safety footwear are typical. Gas leakages are considered accidental occurrences and not a risk encountered during normal procedures. However, eye protection as a precaution is a simple and prudent measure. Taking these factors and the low acute toxicity of ethylene gas into account, it is therefore recommended that for handling the gas cylinders the following PPE should be worn:

- Eye protection and suitable protective gloves.

B.6.14.2 Bystander exposure (IIIA 7.2.2)

As the treatment is made indoors in sealed rooms members of the public will not be present at the site of application. However, workers, who may not be not directly involved in the treatment operation, may be working close to areas where a treatment is taking place and could be exposed via leakages from stores via door seals (the label states the ripening room should be reasonably air-tight). Bystander exposure could also occur during the venting of the gas into the atmosphere after treatment.

No information is available to quantify these potential sources of exposure for bystanders.

B.6.14.3 Worker exposure (IIIA 7.2.3)

The automated nature of the treatment process means entry into treatment rooms is prevented until treatment has been completed and the room ventilated. Workers may then enter the rooms for inspection tasks or maintenance purposes. The exposure levels experienced by these workers will be largely dependent on the efficient functioning of the ventilation system.

Personal and stationary monitoring of ethylene in a company where this gas was used for controlling the ripening of bananas showed air concentrations (after ventilation of the treatment room) to be in the range of 0.02-3.85 mg/m^3 (0.02-3.35 ppm) with an estimated average concentration of 0.35 mg/m^3 (0.3 ppm).

(Tornqvist *et al* , 1989a/IARC)

B.6.14.4 Conclusions

In the absence of appropriate data it is not possible to quantify the exposure to ethylene which might be experienced by operators handling and changing cylinders, but due to the design of the systems involved, this is expected to be minimal under normal circumstances. It is prudent to mitigate any risk of physical injury and from an accidental release by the use of appropriate PPE (gloves and eye protection). RPE may be identified as necessary in some circumstances, for example when entering areas with unknown concentrations of ethylene.

There is uncertainty with regards to the levels of exposure which might be experienced by bystanders either due to leakages during treatment or during ventilation of the treatment room and by workers re-entering treated stores after ventilation as only limited exposure data are available. In a Swedish petrochemical plant (B.6.9.1) eleven workers exposed to levels of ethylene between 0.1 and 4 mg/m^3 showed dose-related increases in haemoglobin adduct formation. A study of fruit store workers (B.6.8.3.5) exposed to ethylene concentrations of 0.02-3.35 ppm showed similar increases in adjunct levels in relation to the control subjects. The concentrations which appear to have produced these effects are similar to the atmospheric concentrations of ethylene measured in fruit stores where ethylene has been used in the manner proposed (B.6.14.3). The presence of the haemoglobin adducts is evidence that some exposure to ethylene (and subsequently the oxide) has occurred. The significance of this exposure is unclear. However, there is some evidence that adduct levels occurring in fruit store workers are similar to the background levels measured in other sections of the population (refer to Table B.6.5). There is also evidence that dietary intake of ethylene may involve acute exposure to much higher concentrations than those encountered in fruit stores after venting; for instance, fully ripe pears may produce internal concentrations of the order of 40 ppm (Wang and Mellenthin, 1972).

In conclusion, the supported use for fruit ripening involves practical steps to minimise exposure to ethylene. The actual levels of exposure for fruit store workers are uncertain. Whilst treatment is essentially an automated, closed, operation, exposure levels for workers are expected to vary between fruit stores, i.e. some stores will be more airtight than others and some will be fitted with better ventilation systems. Member States may wish to investigate these exposure levels further.

資料　11

環境基準に関するテキサス州委員会：サポート文書最終版
エチレン
2008 年４月

Development Support Document
Final, April 15, 2008

Ethylene

CAS Registry Number: 74-85-1

Development Support Document
Final, April 15, 2008

Ethylene

CAS Registry Number: 74-85-1

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TEXAS COMMISSION ON ENVIRONMENTAL QUALITY

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Chapter 1 Summary Tables

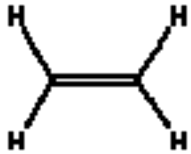
Table 1 provides a summary of health- and welfare-based values resulting from an acute and chronic evaluation of ethylene. Table 2 provides summary information of ethylene's physical/chemical data.

Table 1. Health - and Welfare-Based Values

Short-Term Values	Concentration	Notes
$^{acute}ESL_{veg}$	1,400 µg/m^3 (1,200 ppb) * **Short-Term ESL for Air Permit Reviews**	This value is a sub-threshold concentration that is protective of all crop plants including flowering plants
$^{acute}ESL$ [1 h] (HQ = 0.3)	170,000 µg/m^3 (150,000 ppb)	**Critical Effect**: hepatic damage in male Holtzman rats, based on a free-standing NOAEL
acute ReV (HQ = 1.0)	570,000 µg/m^3 (500,000 ppb) *	
$^{acute}ESL_{odor}$	310,000 µg/m^3 (270,000 ppb) *	50% odor detection threshold
Long-Term Values	**Concentration**	**Notes**
$^{chronic}ESL_{veg}$	34 µg/m^3 (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
$^{chronic}ESL_{nonlinear(nc)}$ (HQ = 0.3)	1,800 µg/m^3 (1,600 ppb)	**Critical Effect**: hepatic damage in Fischer 344 rats based on free-standing NOAEL
chronic ReV (HQ = 1.0)	6,100 µg/m^3 (5,300 ppb) *	
$^{chronic}ESL_{linear(c)}$ $^{chronic}ESL_{nonlinear(c)}$	---	No evidence of carcinogenic potential

* Values that may be used for evaluation of air monitoring data

Abbreviations used: **ppb**, parts per billion; **µg/m^3**, micrograms per cubic meter; **h**, hour; **ESL**, Effects Screening Levels; **ReV**, Reference Value; **^{acute}ESL,** acute health-based ESL; **^{acute}ESL$_{odor}$**, acute odor-based ESL; **^{acute}ESL$_{veg}$**, acute vegetation-based ESL; **^{chronic}ESL$_{nonlinear(nc)}$,** chronic health-based ESL for nonlinear dose-response noncancer effects, **^{chronic}ESL$_{linear(c)}$**, chronic health-based ESL for linear dose-response cancer effects; **^{chronic}ESL$_{nonlinear(c)}$**, chronic health-based ESL for nonlinear dose-response cancer effect; and **^{chronic}ESL$_{veg}$**, chronic vegetation-based ESL; **HQ**, Hazard Quotient.; **NOAEL**, no-observed-adverse-effect level

Table 2. Chemical and Physical Data		
Parameter	**Value**	**Reference**
Molecular Structure		ChemFinder 2004
Molecular Formula	C_2H_4	ChemFinder 2004
Molecular Weight	28.05	ChemFinder, 2004
Physical State	Volatile gas, highly flammable and a dangerous fire risk, liquid under pressure	ACGIH 2005[a], ACC 2004[b]
Color	Colorless	ACGIH 2005[a], ACC 2004[b]
Odor	Faint Sweet	ACGIH 2005[a], ACC 2004[b]
CAS Registry Number	74-85-1	ACGIH 2005[a], ACC 2004[b]
Synonyms	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[b]
Solubility in water	26 g/L- Slightly soluble	ChemFinder 2004
Log K_{ow} or P_{ow}	Log P_{ow}= 1.13	ACC 2004[b]
Vapor Pressure	760 mmHg @ -104°C	Matheson Tri-Gas[c]
Relative Vapor Density @ 32º F (gas; air =1)	0.975	ACC 2004[b]
Density (liquid) @ Critical Temperature (48.54 ºF)	13.36 lb/ft^3; 1.786 lb/gal; 0.21 g/cm^3	ACC 2004[b]
Melting Point	-169.14°C	ChemFinder 2004
Boiling Point	-103.7°C	ChemFinder 2004
Conversion Factors at 25ºC and 1 atmosphere	1 ppb = 1.15 µg/m^3 1 µg/m^3 = 0.87 ppb	Alberta Environment 2003 Toxicology Section

[a]American Conference of Governmental Industrial Hygienists (ACGIH)
[b]American Chemistry Council (ACC) 2004
[c]Matheson Tri-Gas Material Safety Data Sheet

Chapter 2 Major Uses and Sources

Ethylene is produced through both natural and anthropogenic activity. Microbes and higher plants naturally produce ethylene. Ethylene is also released during forest fires and active volcanic events. In higher plants, ethylene functions as a plant hormone and ethylene production can either increase or decrease in response to a variety of environmental stressors such as flooding, wounding (e.g., mechanical and/or pathogenic attack), chemical exposure (e.g., ozone), and mechanical bending (*e.g.,* lodging) (Health Canada 2001).

Ethylene is also 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). However, ethylene production in mammals is only a minor contributor to atmospheric ethylene when compared to the relative contribution from microbial, vegetative, and industrial sources (Health Canada 2001).

In occupational settings, very high concentrations of ethylene can lower oxygen concentrations and has been reported to function as an asphixiant (Cavender 1994). Ethylene is primarily used as an intermediate in the production of other chemicals and as an agent to enhance the ripening process of fruits, vegetables, and flowers. Ethylene is also a high-production-volume chemical product of the petrochemical industry, produced mainly by the steam-cracking of hydrocarbons. Industrial contribution to ambient ethylene is primarily due to fugitive emissions from stacks, flares, and leaks in pipe fittings that can result in a discontinuous exposure scenario (Health Canada 2001).

Ambient ethylene is also produced during incomplete combustion of biomass and fossil fuels. While gasoline itself does not contain ethylene, the combustion of gasoline causes ethylene to be emitted into the ambient air. A relatively large proportion of ethylene in urban air is due to vehicular traffic emissions (Abeles and Heggestad 1973).

Chapter 3 Acute Evaluation

3.1 Health-Based Acute ReV and ESL

3.1.1 Physical/Chemical Properties and Key Studies

3.1.1.1 Physical/Chemical Properties

Ethylene is a highly-flammable volatile gas that is considered to be a fire hazard at sufficiently high concentrations. It is a colorless gas with a faint sweet odor, is a liquid under pressure, and is slightly soluble in water (Chemfinder 2004). The main physical and chemical properties of ethylene are summarized in Table 2. Ethylene has been reported to be relatively non-toxic, has a low blood-gas partition coefficient and does not accumulate in the body.

3.1.1.2 Essential Data and Key Studies

The inhalation toxicity studies conducted by Conolly et al. (1978) and Guest et al. (1981) were selected as key studies to determine the acute Reference Value (ReV) and the acute Effect Screening Level (^{acute}ESL). The study conducted by Conolly and Jaeger (1977) was selected as a supporting study.

3.1.1.2.1 Conolly et al. (1978)

In the Conolly et al. (1978) studies, a group of male Holtzman rats were exposed to 10,000, 25,000, or 50,000 ppm ethylene for 4 h. A second group of rats were administered a combined exposure protocol with polychlorinated biphenyl (PCB) mixture (300 µmoles of PCB/kg of body weight) *via* gavage once daily for 3 days followed by 4 h of inhalation exposure to the various concentrations of ethylene. In addition, control groups were included with rats exposed to PCB alone.

In the study, hepatic damage was assessed by conducting histopathology of the liver and by measuring the levels of hepatic enzymes including sorbitol dehydrogenase (SDH) and serum alanine-alpha-ketoglutarate transaminase (SAKT). Elevated levels of SAKT and SDH are often indicative of liver damage. The authors reported ethylene concentrations at 10,000 ppm to be hepatotoxic only when the rats were pre-treated with the PCB mixture. Specifically, rats that were exposed to ethylene after exposure to PCB mixture were reported to have elevated levels of SDH and the liver of the rats had severe degenerative necrosis.

The authors reported no increase in hepatic enzymes and no liver damage in rats exposed to ethylene alone. A no-observed-adverse-effect-level (NOAEL) of 50,000 ppm was determined from the exposure group of rats exposed only to ethylene. As the studies did not provide any other toxicological information, such as lowest-observed-adverse-effect-level (LOAEL), the NOAEL will be considered a free-standing NOAEL.

3.1.1.2.2 Guest et al. (1981)

Guest et al. (1981) also studied the toxicity of ethylene alone and in conjunction with PCBs. For the ethylene-only exposure group, the authors exposed Fisher rats for 5 h to 10,000 ppm ethylene. For the combined exposure (i.e., PCB mixture + ethylene), the authors administered 500 mg/kg PCB mixture *via* gavage five days prior to exposing the rats for 5 h to 10,000 ppm of ethylene. Control groups included rats exposed either to ethylene alone or rats exposed to only the PCB mixture.

Similar to the Conolly et al. studies, Guest et al. (1981) reported no increase in serum enzyme activities and no necrotic tissue for the ethylene only exposure groups. Exposure only to the PCB mixture, without subsequent exposure to ethylene, resulted in slight hypertrophy of centrolobular liver cells with no hepatocellular necrosis. However, animals exposed to 10,000 ppm ethylene after pre-treatment with the PCB mixture, had uniform hepatic centrolobular necrosis. In addition, the authors also reported elevated hepatic enzyme levels in the combined exposure group (PCB mixture + 10,000 ppm ethylene). As no LOAEL information was available, a free-standing NOAEL of 10,000 ppm was determined from the group exposed only to ethylene.

The results from the acute exposure studies indicate that very high doses of ethylene coupled with high doses of the PCB mixture are required to elicit hepatotoxic responses in rats. Guest et al. (1981) hypothesized that the PCB mixture induced the hepatic mixed-function oxidase (MFO) system that then resulted in hepatotoxicity in the rats.

3.1.1.2.3 Conolly and Jaeger (1977)

The study conducted by Conolly and Jaeger (1977) was selected as a supporting study. Similar to Conolloy et al. (1978) studies, Conolly and Jaeger (1977) studied the acute hepatotoxicity of ethylene and other chemicals with and without PCB pre-treatment. Male Holtzman rates were exposed up to 50,000 ppm ethylene. In addition to hepatic injury, the authors also studied the effects of changes in environmental parameters (i.e., changes in temperature during exposure and food deprivation. The authors reported ethylene to be more acutely toxic in rats that were fasted when compared to rats that were fed and PCB –pre-treated. The authors attribute depletion of glutathione to be higher in the fasted rats.

3.1.1.2.4 Other Studies Reviewed by TS

Aveyard and Collins (1997) conducted a reproductive/developmental toxicity screening study with head only exposures to rats. A total of 10 animals/sex/group were exposed to 5,000 ppm of ethylene for 6 h/day for 2 weeks prior to mating and during the mating period. Female rats were also exposed to ethylene until gestational day 20. No effects on weight gain, food intake, fertility, fecundity, sex ratio, and pup weight or pup growth were reported. This study was described in the Organization for Economic Co-Operation and Development (OECD) dossier on ethylene.

3.1.2 Mode-of-Action (MOA) Analysis and Dose Metric

Ethylene is metabolically converted to ethylene oxide (EtO) *via* the cytochrome P-450 pathway (Filser and Bolt 1983). Concern about the potential toxicity of ethylene stems from the fact that EtO is a suspected human carcinogen and a genotoxicant (ACGIH 2005 and Tornqvist 1994). In addition, EtO is also a potent alkylating agent and can form adducts by interacting with cellular macromolecules such as DNA, RNA, and protein (e.g., hemoglobin). Similar adduct formation has been reported on direct exposure to EtO (ACGIH 2005).

While adducts have been used as biomarkers of DNA damage, their use is controversial. There is some controversy in regards to whether adduct formation is indicative of exposure, and if adducts can be unequivocally utilized as precursors of diseases such as cancer (Selinski et al. 2000). A few studies reported the detection of hemoglobin adduct formation on exposure to ethylene. One example is the identification of hemoglobin adducts (i.e., hydroxyethylvaline adducts) in the serum of fruit storage workers exposed to approximately 0.3 ppm ethylene (Tornquist et al. 1989). Similar results have also been reported in plastic industry workers exposed to ethylene (Granath et al. 1996).

Very few human exposure studies using ethylene have been conducted. The majority of ethylene exposure studies have been conducted using animals. When using animal studies, it is beneficial to extrapolate the risks observed in animals to humans using physiologically-based-pharmacokinetic (PBPK) models. Filser et al. (1992) measured ethylene uptake by exposing 6 human subjects for 2 h in controlled chambers to 5 and 50 ppm of ethylene. The authors reported 98% of the ethylene to be exhaled

unchanged and only 2% of the ethylene was absorbed and metabolized to EtO. Similar to humans, most of the inhaled ethylene (83%) in rats was exhaled unchanged. Further, the relatively smaller fraction of ethylene that was actually absorbed was also reported to be eliminated unchanged in rats (Filser and Bolt 1983).

The metabolic conversion of ethylene to EtO has been reported to be a rate-limiting step resulting in only an insignificant amount of EtO being produced during the process (Bolt and Filser 1987 and Csanady et al. 2000). At 37 ppm ethylene exposure in rats, Bolt and Filser (1987) estimated a 1 ppm equivalent exposure to EtO in humans, while Csanady et al. (2000) have reported an exposure of 45 ppm ethylene in rats to be equivalent to a 1 ppm EtO exposure in humans.

3.1.3 Points of Departure (PODs) for the Key Studies

A POD of 50,000 ppm based on a free-standing NOAEL was determined from the Conolly et al. studies, and a POD of 10,000 ppm based on a free-standing NOAEL was determined from the Guest et al. (1981) study. In the toxicity study selected as the key study, data on the exposure concentration of the parent chemical are available. Since the MOA of the toxic response is not fully understood and data on other more specific dose metrics are not available (e.g. blood concentration of parent chemical, area under blood concentration curve of parent chemical, or putative metabolite concentrations in blood or target tissue), the exposure concentration of the parent chemical was used as the default dose metric.

3.1.4 Dosimetric Adjustments

3.1.4.1 Default Exposure Duration Adjustments

In accordance to the ESL Guidelines, a duration adjustment for 1 h is recommended if the data are obtained from acute toxicity studies with greater than 1 h exposure (TCEQ 2006). However, as the reported PODs in the key studies were relatively very high (i.e., indicative of low toxicity) and because no adverse effects were observed in the key studies at either the 4 h and/or 5 h study, the Toxicology Section (TS), did not conduct duration adjustments and considered the POD for 1 h to be the same as the POD determined for exposure durations greater than 1 h (i.e., 50,000 ppm from the Conolly et al. and 10,000 ppm from the Guest et al. (1981) study).

The POD determined from the Conolly et al. studies (50,000 ppm) is higher than the POD determined from the Guest et al. (1981) study and is selected by the TS as the POD to derive a health-based acute reference value (acute ReV) and effects screening level (ESL). The TS selected the higher POD based on the fact that the key and supporting studies only determined a free-standing NOAEL and on US. EPA's (2002) definition of a NOAEL,"The highest exposure level at which there are no biologically significant increases in the frequency or severity of adverse effect between the exposed population and its appropriate control". Some effects may be produced at this level, but they are not considered adverse or precursors to adverse effects".

3.1.4.2 Default Dosimetry Duration Adjustments from Animal-to-Human Exposure

As no duration adjustments are required, the POD becomes POD_{ADJ} and is 50,000 ppm. The POD_{ADJ} is then adjusted to human equivalent POD or $POD_{HEC.}$ Ethylene is relatively non-toxic even at high concentrations as it does not produce point of entry (POE) respiratory effects and the critical effect is

hepatotoxicity. The TS will consider ethylene as a Category 3 gas and the duration exposure adjustments from animals to humans will be conducted with the following equation:

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

Where,
POD_{HEC} = Point of Departure at Human Equivalent Concentration
POD_{ADJ} = Adjusted Point of Departure
$H_{b/g}$ = Ratio of blood:gas partition coefficient
A = Animal
H = Human

According to USEPA (1994), if the animal blood:gas partition coefficient is greater than the human blood:gas partition coefficient, a default value of 1 is used for the regional gas dose ratio $[(H_{b/g})_A / (H_{b/g})_H]$, (RGDR). Csanady (2000) reported the tissue:air partition coefficients for rat and humans to be very similar and the blood:gas partition coefficients for rats to be double that of human values. The TS will therefore conservatively consider a default blood:gas partition coefficient of 1. The POD_{HEC} calculated based on the Conolly et al. studies is:

$POD_{HEC} = POD_{ADJ} \times (H_{b/g})_A / (H_{b/g})_H$
POD_{HEC} = 50,000 ppm x 1
POD_{HEC} = 50,000 ppm

3.1.5 Critical Effect and Adjustments of the POD_{HEC}

3.1.5.1 Critical Effect

Potential hepatotoxicity is the critical effect in the animal studies discussed in Section 3.1.1.2, although the POD_{HEC} is a free-standing NOAEL, and no adverse effects were noted in any ethylene-only exposure group.

3.1.5.2 Uncertainty Factors (UFs)

The TS applied the following UFs to the POD_{HEC} of 50,000 ppm to derive an acute Reference Value (acute ReV) under the assumption of a threshold/nonlinear MOA in accordance with the ESL Guidelines (TCEQ 2006). For detailed information on the MOA, please see Section 3.1.2. A interspecies UF of 3 was applied to account for extrapolation from animals to humans (UF_A), a UF of 10 is applied to account for intraspecies variability (UF_H), and a database UF of 3 was applied to account for deficiencies in the database (medium database confidence) of the referenced studies (UF_D). A total UF of 100 (i.e., 3 x 10 x 3 = 100) was applied to POD_{HEC} of 50,000 ppm.

acute ReV = $POD_{HEC} / (UF_A \times UF_H \times UF_D)$
= 50,000 ppm/(3 x 10 x 3)
= 50,000 ppm/100
= 500 ppm (500,000 ppb or 570,000 µg/m^3)

A UF_A of 3 was used because default dosimetric adjustments from animal-to-human exposure were conducted which accounts for toxicokinetic differences but not toxicodynamic differences. A UF_H of 10 was used to account for potentially sensitive subpopulations, and a UF_D of 3 was used because of the availability of several toxicity studies with a wide range of end points The confidence in the acute database is medium.

3.1.6 Health-Based Acute ReV and ^{acute} ESL

As discussed in the previous section, UFs were applied to the POD obtained from the Conolly et al. studies to derive the acute ReV. The acute ReV was rounded to two significant figures. Rounding to two significant figures, the 1-h acute ReV is 500,000 ppb (570,000 µg/m^3) The rounded acute ReV was then used to calculate the ^{acute}ESL using a target hazard quotient of 0.3 (Table 3).

^{acute}ESL = 0.3 x acute ReV
^{acute}ESL = 0.3 x 500,000 ppb
^{acute}ESL = 150,000 ppb (170,000 µg/m^3)

Table 3. Derivation of the Acute ReV and ^{acute}ESL	
Key Studies	Conolly et al. (1978)
Study population	Male Holtzman rats
Study quality	Medium-high
Exposure Method	Inhalation
Critical Effects	Hepatic effects
POD (original animal study) NOAEL	50,000 ppm (free-standing NOAEL)
POD_{ADJ} (No adjustment necessary)	50,000 ppm
POD_{HEC}	50,000 ppm (gas with systemic effects based on default RGDR =1)
Exposure Duration	4 h
Total Uncertainty Factors (UFs)	100
Interspecies UF	3
Intraspecies UF	10
LOAEL UF	Not applicable
Incomplete Database UF *Database Quality*	3 Medium
acute Rev[1hr] (HQ = 1)	**570,000 µg/m^3 (500,000 ppb)**
^{acute} ESL [1h] (HQ= 0.3)	**170,000 µg/m^3 (150,000 ppb)**

3.1.7 Information from Other Organizations

The USEPA Office of Prevention, Pesticides and Toxic Substances has reported the maximum exposure rate to ethylene under current use as a pesticide to be 1000 ppm (USEPA 1992). This limit is for the post-harvest exposure of stored commodities (USEPA 1992). The Screening Information Data Set (SIDS) program operated under the auspices of the Organization for Economic Cooperation and Development recommends no further testing of ethylene toxicity based on the reports of low toxicity of ethylene and no

risk to human health either through direct exposure or through indirect exposure *via* the environment (OECD SIDS 1994).

3.2. Welfare-Based Acute ESLs

3.2.1 Odor Perception

Ethylene has a sweet odor and taste. The ACGIH (2005) reported odor threshold is 290,000 ppb and is based on the Amoore and Hautala (1983) study. A 50% odor detection value of 310,000 µg/m^3 (270,000 ppb) has also been reported by Hellman and Small (1974). Since, Hellman and Small (1974) is included in the list of acceptable sources for odor threshold values and is listed in Appendix B of the ESL Guidelines (TCEQ 2006), the $^{acute}ESL_{odor}$ is 310,000 µg/m^3 (270,000 ppb).

3.2.2 Vegetation Effects

3.2.2.1 Summary of Ethylene Induced Vegetative Effects

Interest in ethylene research spiked when it was identified to be phytotoxic to greenhouse plants (Crocker 1948). Later, many investigators documented the adverse effects of ethylene on plant species (Darley et al. 1963, Air Quality Criteria for Hydrocarbons 1970) and reported the effects of ethylene to be dependent on the types of plant species and the stage of plant growth (Tonneijck et al. 2003, Reid and Watson 1985). Fruits (e.g., apples, oranges, and avocados) release ethylene as they approach maturity which in turn promotes the ripening of the fruits.

The majority of ethylene research has been conducted in growth chambers and very few studies exist for field grown plants. Abeles et al. (1992) reported 10 ppb as the threshold concentration for physiological effects from studies in greenhouse experiments with ethylene. However, there is some controversy regarding the relevance of the threshold concentrations reported by Abeles et al. (1992) to field grown plants. Amongst the issues surrounding the applicability of the results reported by Abeles et al. (1992) is the fact that greenhouse plants are normally exposed to very high concentrations of ethylene in a continuous manner. Field grown plants generally experience lower concentrations of ethylene and the exposure pattern is said to be discontinuous (Tonneijck et al. 1999, 2000, and Dueck et al. 2004). Greenhouse plants are also less hardy when compared to the field-grown plants and, may experience more adverse effects (Tonneijck et al. 2003).

Ethylene is a plant hormone that is produced naturally at many of the stages of plant growth. As a plant hormone, ethylene has been reported to regulate both the morphological (e.g., leaf abscission and epinasty (leaf curling)) and physiological effects (e.g., bud formation, inhibition of flowering, photosynthesis, senescence, sprouting of buds, seed germination, and flower formation). In addition, ethylene can stimulate or inhibit the growth process, influence other plant hormones (e.g., giberillic acid), or itself be influenced by other hormones (Grossmann and Hansen 2001).

Tonneijck et al. (2000) reported epinasty or leaf curling in potatoes grown in the vicinity of polyethylene manufacturing plants. However, the authors reported that the epinasty did not translate to a loss in tuber yield. In a review on the effects of air-borne volatile organic compounds such as ethylene, Cape (2003) reported epinasty to be a reversible effect if the exposure ended. Nutritional deficiencies and stress factors (i.e., water stress, temperatures, and diseases) can cause vegetative effects (i.e., leaf and flower

abscission) that are similar to the effects caused by exogenous ethylene. Also, plants undergoing stress are reported to be more susceptible to ethylene (Munne-Bosch et al. 2004, Guinn 1982, and Jordan et al. 1972). It therefore becomes difficult to differentiate subtle physiological and morphological effects caused by naturally produced ethylene (i.e., endogenous) versus ambient ethylene (i.e., exogenous).

Fugitive emissions from leaks around industrial facilities and vehicular traffic can create a discontinuous exposure scenario in the ambient environment. Meteorological factors (i.e., wind direction and velocity) can further aid in the movement and dispersal of the emissions and result in subsequent exposures to field-grown plants. During the discontinuous exposure, field-grown plants often have a chance to recover from the exposure. Green-house plants on the other hand are constantly exposed to ethylene from generators that are housed within the green-houses. For this reason, Tonneijck et al. (2003) indicated that the field-grown plants may be less responsive to ethylene when compared to the greenhouse plants where continuous exposure is the norm.

3.2.2.2 Summary of Ethylene Induced Effects in Flowering plants

Many investigators consider flowering plants such as petunias (*Petunia nyctaginiflora*), marigolds (*Tagetes erecta*), orchids (*Cattleya spp*), and carnations (*Dianthus caryophyllus L.*) to be sensitive to ethylene (Tonneijck et al. 2003, Posthumus 1983, and Davidson 1949). Leaf senecessence and flower abscission have been reported to occur due to ethylene exposure (Tonneijck et al. 2003). In addition, decreased flower size and increased abortion of flower buds in petunias have been used as indicators of plant response to pollution (Posthumus 1983 and Cape 2004). While petunias have been used as indicator plants to assess ethylene sensitivity, orchids have been reported to exhibit severe dry sepal injury at exposures of 100 ppb of ethylene for up to 8 h (Davidson, 1949).

The flowering plant studies are limited by the fact that they often included relatively high ethylene exposure concentrations (2 to 4 ppm) when compared to what is expected in an ambient setting (Underwood et al. 2005, Onozaki et al. 2004, Woodson et al. 1988). Ambient ethylene levels vary widely. For example, while the median concentration of ethylene was reported to be 10.79 ppb in 39 US cities from 1984 – 1985 (Seila et al. 1989), Abeles and Heggestad (1973) reported a maximum value of 700 ppb of ethylene in Washington DC. In some of the reported flowering plant studies, longer exposure durations ($\geq$ 8 and/or $\geq$ 12 h) were required before adverse effects could be recorded. In a multi-year study conducted by Tonneijck et al. (2003), a quantitative relationship between short-term ethylene exposure and plant response was not adequately addressed. In another short-term exposure study, excised flowering petunias were exposed to 4 ppm ethylene for 0, 2, 4, 8, or 10 h (Underwood et al. 2005). Similar exposure protocols with excised flowers were reported in carnations and geraniums (Evensen K 1991). While the more recent ethylene exposure studies in flowering plants included adequate dose-response information, the inclusion of excised flowers in the exposure protocols in the opinion of TS is not an appropriate scenario to depict normal vegetation conditions. For this reason, TS has not chosen these flowering plant studies as key studies for the development of the short-term vegetation ESL.

Woltering and Van Doorn (1988) conducted an extensive assessment of ethylene flower sensitivity amongst 93 species of plants from 22 plant families. However, the study included high exposure concentrations (3,405 $\mu g/m^3$) that are not relevant to ambient conditions. In addition, the reported exposure durations (22-24 h) were greater than the acute exposure scenarios defined in the ESL guidelines (TCEQ 2006). As such, the TS have not chosen the study conducted by Woltering and Van Doorn (1988) as a key study for the development of the short-term vegetation ESL for ethylene.

3.2.2.3 Key Studies

Since ethylene-related vegetative effects have been documented, a short-term vegetative based ESL for ethylene exposure was determined according to the ESL Guidelines (TCEQ 2006). The Alberta Canada's Ethylene Research Project (i.e., The Alberta Canada Study) was identified as a key study and the study conducted by Pallas and Kays (1982) was identified as a supporting study to develop the vegetation based acute ESL ($^{acute}ESL_{veg}$).

3.2.2.3.1 The Alberta Canada Study

The Alberta Canada Study was a multi-stake holder initiative that was jointly sponsored by the Provisional Government and petrochemical industries in Alberta, Canada (Alberta Research Council 2001). The project was initiated to determine the concentration threshold at which short-term exposures to ethylene would cause significant effects on vegetative and reproductive parameters in selected cultivars of agricultural crops of interest to Alberta, Canada. Archambault and Li, the investigators of the Alberta Canada study, conducted extensive preliminary screening experiments with Ethephon ((2-Chloroethyl) phosphonic acid) to determine which plant species in each of 3 plant categories (i.e., cereal, legumes, and oilseeds) and 2 tree species were most sensitive to ethylene (Archambault et al. 2006, Archambault and Li 2001, 1999a, and 1999b). In their studies with field crops, sensitivity of seed yield to ethylene was the critical effect that was used to determine the relative sensitivity of the crop species. However, for the tree species, sensitivity to ethylene was based on the vegetative characteristics because vegetative characteristics are important parameters that determine the marketability of seedlings.

Table 4: Information on the Plants and Trees included in the Alberta Canada Study

Category	Plant	Species	Sensitive Stage of Growth	Vegetative Effects
Cereal	Barley	*Hordeum vulgare* cv. Harrington	Spike emerging stage	Decrease in photosynthesis, vegetative effects, and decreases in seed yield.
Legumes	Field pea	*Pisum sativum* cv. Carrera	Flat pod stage	
Oilseeds	Canola	*Brassica napus* cv. Quantum	Many flowers open stage	
Trees	White spruce	*Picea gluca*	Vegetative growth	Effects on seed germination, seedling vigor, growth, and seedling marketability.
Trees	Lodgepole pine	*Pinus Contorta*		

Information on the plants and trees included in the Alberta Canada Study is provided in Table 4. All the plants included in the experiment were grown in the greenhouse until the appropriate stage was reached at which time they were transferred to exposure chambers and left for one day to acclimate prior to the start of the exposures. Plants were moved back to the greenhouse and grown to maturity after exposures were completed. For a detailed description of the treatments and exposure regimens, please see the Alberta's Ethylene Crop Research Project Report titled, "Response of Barley, Field peas, Canola, and Tree seedlings to Ethylene Exposure (2001)".

Treatments included exposing barley, field pea, canola, white spruce, and lodgepole pine to six concentrations of ethylene (10, 75, 150, 300, 600, and 1,200 ppb) at four exposure durations (1.5, 3, 6, and 12 h). In their studies, the investigators defined short-term exposures as being equal to or less than 12 h. In all the experiments, the order of exposures was randomly selected. In addition, the investigators of the Alberta Canada Study considered the 10 ppb exposure concentration as a background concentration based on the findings by Reid and Watson (1985), who reported that complete removal of ethylene from atmosphere would lead to detrimental effects on plant growth.

The investigators of the Alberta Canada Study reported barley from the cereal category, field pea from the legume category, and canola from the oil seed category to be the most sensitive species in their respective categories. In addition, the investigators also reported white spruce and lodgepole pine to be the most sensitive tree species for ethylene exposure.

The investigators conducted analysis of variance (ANOVA) and reported no significant effects on photosynthetic rates or vegetative, or reproductive effects for all exposure durations (up to 12 h) at all the exposure concentrations (up to 1,200 ppb) for all the plant species (barley, field peas, and canola). In the case of the trees (i.e., lodge pine and white spruce), the investigators reported no effects on seed germination, seedling vigor, growth, or seedling marketability after an exposure to 1,200 ppb of ethylene for exposure durations up to 12 h. The investigators reported that after short-term exposures (≤ 12 h) the plants and trees recovered from decreases in photosynthesis and growth.

In addition, the investigators also conducted additional statistical analysis (e.g., linear regression) to further understand the relationship between several plant parameters and ethylene dose expressed as a product of ethylene concentration (ppb) and exposure duration (h). The investigators reported a poor correlation between the various plant parameters measured and the ethylene dose. In the case of the tree seeds/seedlings, the investigators reported a poor correlation between germination and ethylene indicating that there was no significant dose effect.

However, the Alberta Research Council established a different short-term (i.e., 1-h) Ambient Air Quality Objective when compared to the results of the Alberta Canada Study. The Alberta Research Council established a short-term Ambient Air Quality Objective of 1,200 $\mu g/m^3$ (1,044 ppb) to be protective of all plant species (Alberta Research Council Report 2001).

3.2.2.3.2 Pallas and Kays (1982) Study

Pallas and Kays (1982) studied the effect of ethylene on photosynthesis by exposing leaves of a variety of plants to 1 microliter per liter (µl/L) or 1,000 ppb of ethylene for 0, 0.25, 0.5, 1, 2, 4, and 6 h (Table 5). The investigators also reported including a day without treatment between the treatments to measure any "carry-over effects" on photosynthesis. The Pallas and Kays study (1982) is a well-conducted study as the inhibition of photosynthesis was examined in many plants at exposure durations representative of short-term exposure scenarios. However, in the TS's opinion, the study is limited because it included only a single exposure concentration (1,000 ppb). For this reason, the TS considered the Pallas and Kays (1982) study as a supporting study to develop the $^{acute}ESL_{veg}$.

Table 5: Information on the Plants Included in the Pallas and Kays Study	
Green bean	*Phaseolus vulgaris* L. cv. Contender
Pea	*Pisum sativum* L. cv. Wando
Peanut	*Arachis hypogea* L. cv. Florunner
Scarlet runner bean	*Phaseolus coccineus* L.
Sensitive plant (according to the study authors)	*Mimosa Pudica L.*
Irish Potato	*Solanum tuberosum* L.
Sunflower	*Helianthus annus* L. line CM90RR
White Clover	*Trifolium repens L.*
Jerusalem artichoke	*Helianthus tuberosus* L.

Pallas and Kays (1982) reported a wide range of responses in photosynthesis amongst the various cultivars exposed to ethylene. The net decrease in photosynthesis was dependent both on the genotype of the cultivar and the exposure duration. Pallas and Kays (1982) reported a decrease in photosynthesis with an increase in the exposure duration from 0.25 to 6 h in peanuts. In addition, the authors also reported a net decrease in photosynthesis when Jerusalem artichoke, sunflower, and sweet potato were exposed to 1,000 ppb ethylene for 2.5 h. However, the authors reported no effects on photosynthesis in green bean, scarlet runner bean, pea, Irish potato, or white clover. Amongst the various plant species tested in the study, peanut cultivars were reported to be relatively more sensitive to ethylene exposure. With an increase in the duration of exposure, the inhibitory effect on photosynthesis increased, especially for peanut. Pallas and Kays (1982) reported a 68% decrease in photosynthesis after a 6 h exposure period. However, the investigators also reported a rapid recovery after short–term exposure durations and the plants did not exhibit any carry-over effect on photosynthesis. The photosynthetic rates after the short-term exposure treatments (0.5 - 6 h) returned to normal or pre-exposure levels within 24 h following treatments. Plants in the 6 h treatment required an additional day for recovery. Overall, Pallas and Kays (1982) concluded the decrease in photosynthesis to be a reversible effect.

3.2.2.4 Derivation of the $^{acute}ESL_{veg}$

According to the ESL Guidelines, $^{acute}ESL_{veg}$ is set at a threshold concentration for adverse effects (TCEQ 2006). However, the results from the Alberta Canada Study and the Pallas and Kays (1982) study indicate that short-term exposures (≤ 12 h and/or ≤ 6 h) of plants to ethylene either at 1,200 ppb or 1,000 ppb respectively to result in no adverse vegetative effects. While the TS acknowledges the absence of adverse vegetative effects at the reported exposure concentrations and durations in both the key and supporting studies, TS conservatively recommends a 1-h $^{acute}ESL_{veg}$ of 1,400 µg/m^3 (1,200 ppb) as a sub-threshold concentration to be protective for all plant species.

The $^{acute}ESL_{veg}$ of 1,400 µg/m^3 was rounded to the two significant figures and is based on the results of the short-term exposures from the Alberta Canada Study (Table 6). In recommending a 1-h $^{acute}ESL_{veg}$ of 1,400 µg/m^3 (1,200 ppb), the TS has taken into consideration that the reported exposure concentration (1,200 ppb) was the highest exposure concentration at exposure durations up to 12 h (i.e., 1.5, 3, 6, and 12 h) and the limited database of well-conducted ethylene exposure field studies for crops. The proposed screening value should also adequately protect vegetation from potential intermittent exposures.

Table 6. Derivation of the acuteESLveg	
Study	Alberta's Ethylene/Crop Research Project Report III
Study population	Barley, field pea, canola, and tree seedlings
Exposure Method	Growth Chambers
Critical Effects	Vegetative effects and decrease in photosynthesis
POD (Sub-Threshold Concentration)	1,400 µg/m3 (1,200 ppb)
Exposure Duration	1.5, 3, 6, 12 h
$^{acute}ESL_{veg}$	**1,400 µg/m3 (1,200 ppb)**

3.3 Short-Term ESL and Values for Air Monitoring Evaluation

The acute evaluation resulted in the derivation of the following acute values:

- $^{acute}ESL_{veg}$ = 1,400 µg/m^3 (1200 ppb)
- acute ReV = 570,000 µg/m^3 (500,000 ppb)
- $^{acute}ESL$ = 170,000 µg/m^3 (150,000 ppb)
- $^{acute}ESL_{odor}$ = 310,000 µg/m^3 (270,000 ppb)

The short-term ESL for air permit reviews and air monitoring evaluations is the $^{acute}ESL_{veg}$ of 1,400 µg/m^3 (1,200 ppb) as it is lower than the $^{acute}ESL$ and the $^{acute}ESL_{odor}$ (Table1). The acute ReV and the $^{acute}ESL_{odor}$ may also be used for air monitoring evaluations. The $^{acute}ESL$ (HQ = 0.3) will not be used by the TS to evaluate air monitoring data.

Chapter 4 Chronic Evaluation

4.1 Noncarcinogenic Potential

4.1.1 Physical/Chemical Properties and Key Studies

Physical/chemical properties of ethylene are discussed in Chapter 3. Due to the unavailability of chronic inhalation exposure studies in humans, the TS selected well-conducted animal studies to develop the chronic ReV. A two-year inhalation study conducted by Hamm et al. (1984) was selected as a key study to determine the chronic ReV. In the study, Hamm et al. (1984) randomly divided 960 Fischer-344 rats into 4 groups of 120 animals for each sex and exposed them to 0, 300, 1,000, or 3,000 ppm of ethylene for 6 h/day, 5 days per week for 106 weeks. There were no reports of any chronic toxicity or oncogenicity at any of the concentrations tested. Comprehensive analysis of various tissues (e.g., kidney and nasal turbinates) indicated no signs of carcinogenic effects. While a variety of proliferative, degenerative, and inflammatory lesions were observed in both the control and treatment groups, the authors reported that these types of lesions are typical of the animal. A discussion on the high concentrations of ethylene is warranted based on previous findings that 3,000 ppm is the highest concentration that could be safely studied for long-term chronic studies (CIIT, 1980). Ethylene is

explosive when it reaches 3% or higher in air composition. However, for acute exposure experiments, investigators were able to use higher concentrations of ethylene safely even up to 50,000 ppm (Section 3.1.3.1). Based on safety issues, Hamm et al. (1984) reported 3,000 ppm as the NOAEL for long-term chronic studies. TS will therefore consider 3,000 ppm as a free-standing NOAEL.

A 90 day sub-chronic study reported by Rhudy et al. (1978) was selected as a supporting study to determine the chronic ReV. Rhudy et al. (1978) exposed Sprague-Dawley rats to various concentrations of ethylene (0, 300, 1,000, 3,000, or 10,000 ppm) for 6 h/day, 5 days/week for 14 weeks. The authors reported no toxic effects related to ethylene exposure on conducting a comprehensive microscopic analysis of tissue specimens. In addition, the authors also did not report any changes or abnormalities in hematology, clinical chemistry, and urinalysis. A free-standing NOAEL of 10,000 ppm was determined from the Rhudy et al. (1978) study.

4.1.2 MOA Analysis and Dose Metric

The MOA of ethylene is described in detail in Section 3.1.2. For the key and supporting studies, data on concentration of the parent chemical is used as the default dose metric.

4.1.3 POD for Key and Supporting Studies

The NOAEL reported in the Rhudy et al. (1978) study (10,000 ppm) was higher than the NOAEL reported in the Hamm et al. (1984) study (3,000 ppm). However, the TS selected the NOAEL (3,000 ppm) from the Hamm et al. (1984) study because it was a chronic, rather than a sub-chronic exposure study.

4.1.3.1 Default Exposure Duration Adjustments

The TS conducted an adjustment from the discontinuous animal exposure regimen to a continuous exposure regimen with the following equation to determine the POD_{ADJ}. The POD_{ADJ} was determined to be 535.71 ppm (see below).

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

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

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

4.1.3.2 Default Dosimetry Adjustments

Similar to section 3.1.4.2, the TS considered ethylene as a Category 3 gas and the duration exposure adjustments from animals to humans was conducted to determine the human equivalent POD or POD_{HEC} with the following equation:

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

Where:

POD_{HEC} = Point of Departure at Human Equivalent Concentration
POD_{ADJ} = Adjusted Point of Departure
$H_{b/g}$ = Ratio of blood: gas partition coefficient
A = Animal
H = Human

The POD_{HEC} based on the Hamm et al. (19784) study:

$POD_{HEC} = POD_{ADJ} \times (H_{b/g})_A / (H_{b/g})_H$
$= 535.71 \text{ ppm} \times 1$
$= 535.71 \text{ ppm}$

4.1.4 Application of Uncertainty Factors to the POD_{HEC} based on MOA Analysis

TS applied appropriate UFs to derive a Chronic ReV in accordance with the ESL Guidelines (TCEQ 2006). The POD_{HEC} of 535.71 ppm is based on a 2-Year study conducted by Hamm et al. (1984). The following UFs are applied: A UF of 3 is applied to account for extrapolation from animals to humans (inter-species variability, UF_A), a UF of 10 is applied to account for intraspecies variability (UF_H), and a UF of 3 to account for deficiencies in the database (UF_A). The total UF was equal to 100 (3 x 10 x 3).

$ReV = POD_{HEC} / (UF_A \times UF_H \times UF_D)$
$ReV = 535.71 \text{ ppm} / (3 \times 10 \times 3)$; $Rev = 535.71 \text{ ppm}/100$
$ReV = 5.3571 \text{ ppm}$ (5,300 ppb or 6,100 $\mu g/m^3$) (rounding up to two significant figure)

A UF_A of 3 was used because default dosimetric adjustments from animal-to-human exposure were conducted which account for toxicokinetic differences but not toxicodynamic differences. A UF_H of 10 was used to account for potentially sensitive subpopulations, and a UF_D of 3 was used because of the availability of well-conducted chronic and sub-chronic toxicity studies with a wide range of end points The confidence in the chronic database is medium.

4.1.5 Health-Based Chronic ReV and $^{chronic}ESL_{nonlinear(nc)}$

The chronic ReV of 6,100 $\mu g/m^3$ (5,300 ppb) rounded to two significant figures was used to calculate the $^{chronic}ESL_{nonlinear(nc)}$ by using the following formula and a hazard quotient (HQ) of 0.3 (Table 7):

$^{chronic}ESL_{nonlinear(nc)}$ = chronic ReV x HQ
$= 5{,}300 \text{ ppb} \times 0.3 = 1{,}600 \text{ ppb}$ (1,800 $\mu g/m^3$)

Table 7. Derivation of the Chronic ReV and $^{chronic}ESL_{nonlinear(nc)}$	
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	Hepatic damage
POD (original animal study)	3,000 ppm, NOAEL
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
Interspecies UF	3
Intraspecies UF	10
LOAEL UF	Not Applicable
Subchronic to chronic UF	Not Applicable
Incomplete Database UF (Database Quality)	3 (Medium)
Chronic ReV (HQ = 1)	**6,100 µg/m^3 (5,300 ppb)**
$^{chronic}ESL_{nonlinear(nc)}$ (HQ = 0.3)	**1,800 µg/m^3 (1,600 ppb)**

4.2 Carcinogenic Potential

Concern over the toxicity of ethylene is due to the metabolic conversion of ethylene to EtO which has been designated as a carcinogen and a genotoxicant (Bolt and Filser 1987). However, the percentage conversion of ethylene to EtO is insignificant (See Section 3.12). According to the ACGIH report published in 2005, "the potential toxicity due to EtO formation from the metabolic conversion of ethylene to EtO will not likely pose a cancer risk based on the current knowledge of the significance of adducts". In conclusion, ethylene is a relatively non-toxic chemical and is assumed to have a threshold, non-linear MOA. ACGIH (2005) has designated ethylene as A4 (i.e., it is not classified as a human carcinogen).

The International Agency for Research on Cancer (IARC) (1994) has classified ethylene as a Group 3, which indicates that it is a not classified as a human carcinogen. The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK Commission) has classified ethylene as a 3B (Deutsche Forschungsgemeinschaft 2004 in ACGIH 2005). The TS has determined that the data are inadequate for an assessment of human carcinogenic potential by the inhalation pathway.

4.3. Welfare-Based Chronic ESL

4.3.1. Development of Vegetation-Based Chronic ESL ($^{chronic}ESL_{veg}$)

Four key studies were identified to determine the $^{chronic}ESL_{veg}$. The first study was the Alberta Ethylene Research Project in which barley, field peas, and canola were exposed to various concentrations of ethylene for different durations (Alberta Canada Study). The second key study was conducted by Klassen and Bugbee (2002) in which they evaluated the sensitivity of wheat (*Triticum aestivum* L.) and rice (*Oryza sativa*) to various concentrations of ethylene. The third study was conducted by Reid and Watson (1985) who examined the sensitivity of oats (*Avena Sativa* L. cv. Random) and canola to chronic exposure to ethylene. In the fourth key study, Blankenship and colleagues (1993) conducted experiments to study the effects of continuous low levels of ethylene on growth and flowering of Eastern lily (*Lillium longiflorum* Thumb. Culitvar 'Nellie White').

4.3.1.1 The Alberta Canada Study

Archambault and Li (2001) wanted to determine the critical duration of exposure and long-term vegetative effects based on yield when plants are exposed to ethylene during a sensitive stage of growth. The Alberta Environment (2003) report includes various ethylene exposure scenarios and is discussed below. For short-term exposure scenarios (less than or equal to 12 h) please see Section 3.4. Two of the exposure scenarios are discussed below. For a detailed description of the treatments and exposure regimens, please see the Alberta's Ethylene Crop Research Project Report titled "Response of Barley, Field Peas, Canola, and Tree Seedlings to Ethylene Exposure (2001)".

Exposure Scenario 1:

In this scenario, Archambault and Li exposed barley plants to 50 ppb of ethylene for 0, 3, 6, 12, 18, and 24 days, and field peas to 50 ppb of ethylene for 0, 12, 16, 20, 24, and 28 days in growth chambers according to standard laboratory protocols. In the case of barley, the seed yield decreased by 41% when the plants were exposed to 50 ppb for 3 days and by 89% when the plants were exposed for 24 days. However, there were no effects on the above ground and root biomass, plant height, or tiller number after exposure to 50 ppb for 24 days. Field peas on the other hand were found to be relatively more insensitive to long-term exposures to ethylene. Exposure of field peas to 50 ppb of ethylene did not result in significant effects in plant height, number of pods, weight of pods, number of seeds, or seed yield. A threshold concentration of 50 ppb for long-term exposures was therefore determined from the studies on barley.

Exposure Scenario 2:

A second exposure protocol included a summary of long-term ethylene exposures in barley, field peas, and canola where barley plants were exposed to a range of ethylene concentrations (10 – 250 ppb). The investigators reported a 63% reduction in seed yield of barley when barley plants were exposed to 34 $\mu g/m^3$ (30 ppb) for 14 days. A threshold concentration of 34 $\mu g/m^3$ (30 ppb) for long-term exposures was therefore determined from the second set of exposure scenarios.

4.3.1.2 Klassen and Bugbee (2002)

Klassen and Bugbee (2002) evaluated the sensitivity of wheat (*Triticum aestivum* L.) and rice (*Oryza sativa*) to continuous ethylene levels ranging from 0 to 1,000 ppb in a growth chamber throughout the growing season. The authors reported anthesis (flowering stage) to be the most sensitive period for the crop plants. Exposures that stopped at the flowering stage were found to have lower reductions in yield. In this experiment, the authors reported that exposure to 50 ppb of ethylene reduced the yield by 36% in wheat and 63% in rice, respectively. In addition, plants that were exposed to 1000 ppb were found to be completely sterile. A threshold concentration of 50 ppb for long-term exposures was therefore determined from the studies on wheat and rice.

4.3.1.3 The Reid and Watson Study (1985)

Reid and Watson (1985) conducted a suite of experiments to determine the effect of various concentrations of ethylene on plant growth in oats (*Avena sativa* L. cv. Random) and canola (*Brassica campestris* L. cv. Candle) plants. Reid and Watson exposed oats for 100 days to 0, 8, 40, 81, and 173 $\mu g/m^3$ of ethylene and canola plants to 0, 12, 40, 173, and 690 $\mu g/m^3$ of ethylene for 87 days. At the 40 $\mu g/m^3$ concentration, the authors reported per plant floret number to decrease by 26% in oats and per plant seed yield to decrease by 57%. The authors therefore reported 40 $\mu g/m^3$ (34 ppb) to be the threshold concentration at which negative effects occur.

4.3.1.4 The Blankenship study (1993)

Blankenship and colleagues (1993) studied the effects of continuous, low levels of ethylene on growth and flowering of Easter lily (*Lilillum longiflorum*) Thumb, cultivar 'Nellie White' by exposing Easter lilies to 0, 0.01, 0.05, or 0.1 µl/l (ppm) ethylene for 77 days. The authors reported that the Easter lilies continuously exposed to 50 ppb (0.05 µl/l) had greater than 50% decrease in dry weight in both shoots and inflorescences. In addition, both the 50 and 100 ppb exposure groups were unmarketable. The plants in the 10 ppb were reported to not be affected and were reported to be marketable. Therefore, the reported threshold concentration for long-term exposure for flowering plants is 50 ppb.

4.3.1.5 Determination of $^{chronic}ESL_{veg}$

Vegetation-based ESLs are set at the threshold concentration for adverse effects and are determined in accordance with ESL Guidelines (TCEQ 2006). Amongst all the key studies identified by the TS, the barley exposure studies (Exposure Scenario 2) reported the lowest threshold concentration of 34 $\mu g/m^3$ (30 ppb). The TS, therefore, determined the $^{chronic}ESL_{veg}$ to be 34 $\mu g/m^3$ (30 ppb).

Table 8. Derivation of the $^{chronic}ESL_{veg}$	
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)	34 µg/m^3 (30 ppb)
Exposure Duration	14 days
$^{chronic}ESL_{veg}$	34 µg/m^3 (30 ppb)

4.3.1.6 Other Vegetation-Based Studies Reviewed by TS

Among crop plants, vegetative effects of cotton (*Gossypium hirsutum*) and potato (*Solanum tuberosum*) have been studied on exposure to ethylene. Hall et al. (1957) reported extensive plant damage in cotton plants in the vicinity of a polyethylene manufacturing plant in Texas. The reported ambient concentrations of ethylene ranged from 0.04 to 30 ppm. In addition to reduction in yield, cotton plants exhibited leaf abscission, scattered seedling death, vine-like growth habit, and abscission of squares. In a growth chamber experiment, Heck et al. (1961) exposed cotton to constant levels of 40 or 100 ppb ethylene for 27 days. While no severe plant injury or death was reported, the authors reported a 25–50% reduction in yield (Heck et al. 1961). Cotton leaf and fruit abscission were also investigated by Hall et al. (1957). TS did not consider these studies as key studies because these studies were reported either in a review article or limited dose-response information was presented.

4.4 Long-Term ESL and Values for Air Monitoring Evaluation

The chronic evaluation resulted in the derivation of the following chronic values:

- $^{chronic}ESL_{veg}$ = 34 µg/m^3 (30 ppb)
- chronic ReV = 6,100 µg/m^3 (5,300 ppb)
- $^{chronic}ESL_{nonlinear(nc)}$ = 1,800 µg/m^3 (1,600 ppb)

The long-term ESL for air permit reviews and air monitoring evaluations is the $^{chronic}ESL_{veg}$ of 34 µg/m^3 (30 ppb). The chronic ReV of 6,100 µg/m^3 (5,300 ppb) may also be used in air monitoring evaluations (Table 1). The $^{chronic}ESL_{nonlinear(nc)}$ (HQ= 0.3) will not be used by the TS to evaluate air monitoring data.

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資料　12

米陸軍健康増進・予防医学センター
野生生物に対するエチレンの毒性評価
2008 年４月

U.S. Army Center for Health Promotion and Preventive Medicine
JANUARY 2006

Wildlife Toxicity Assessment for Ethylene

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USCHPPM

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Prepared by
Health Effects Research Program
Environmental Health Risk Assessment Program

USACHPPM Document No: 37-EJ1138-01Q
Approved for public release; distribution unlimited.

Readiness Thru Health

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Table of Contents

Department of the Army
U.S. Army Center for Health Promotion and Preventive Medicine

Wildlife Toxicity Assessment for Ethylene

CAS No. 74-85-1 **January 2006**

1. Introduction

Ethylene is a colorless gas that is produced by the petrochemical industry in vast quantities throughout the world. As summarized by the International Agency for Research on Cancer (IARC), the compound serves as the "building block" for the production of polyethylene, as well as other important chemicals and intermediates such as ethylene oxide, ethylene dichloride, ethylbenzene, ethylene glycol, ethanol and vinyl acetate monomer among others (IARC 1994). In medicine, the compound has been used as an anaesthetic when mixed with air. However, the use of this formulation has been largely discontinued because of the explosive nature of the ethylene-oxygen mixture. The compound is released to the environment as a product of burning vegetation, a by-product of petroleum refining, through production by steam cracking of hydrocarbon feedstocks, incomplete combustion of fossil fuels, in automobile and diesel exhausts and by sewage treatment plants (HSDB 2001). Ethylene is also produced and emitted by all plants and hence is present naturally in the environment. Human beings and other mammals also produce the compound endogenously.

This Wildlife Toxicity Assessment summarizes current knowledge of the toxicological impacts of ethylene on wildlife. Evaluating the toxicity of ethylene is intended to contribute to the derivation of toxicity reference values (TRVs) that could serve as screening-level benchmarks for wildlife in the vicinity of contaminated sites. The protocol for the performance of this assessment is documented in the U.S. Army Center for Health Promotion and Preventive Medicine Technical Guide 254, *Standard Practice for Wildlife Toxicity Reference Values* (USACHPPM 2000).

2. Toxicity Profile

2.1 Literature Review

Relevant biomedical, toxicological, and ecological databases were electronically searched April 20, 2001 and May 2, 2001, using Dialog to identify primary reports of studies and reviews on the toxicology of ethylene. Separate searches were carried out linking the compound to mammals, birds, and reptiles and amphibians (combined). In general, a two-tiered approach was used in which all citations were first evaluated as titles and “key words in context.” All available abstracts of those articles that were selected

in the first tier as possibly relevant to TRV development were then evaluated for relevancy and retention for evaluation in the second tier. For ethylene, 9 articles were marked for retrieval from 538 initial hits, a disparity arising because the initial sweep captured a substantial number of reports of studies that featured the use of "ethylene" as part of the name of a large number of other compounds. These were eliminated in Tier 2 of the selection process. Details of the search strategies and the results of each are documented in Appendix A.

In addition to Dialog searching, a number of U.S. Army reports were identified in the Defense Technical Information Center (DTIC). Secondary references and sources of information on ethylene included the National Library of Medicine's Hazardous Substances Databank (HSDB 2001) and IARC monographs (IARC 1979, 1994).

2.2 Environmental Fate and Transport

Ethylene is a ubiquitous component of the atmosphere, with concentrations reaching 5 $\mu g/m^3$ at remote sites. However, its concentration can range greater than 1000 $\mu g/m^3$ in urban centers, largely as a result of vehicle exhaust emissions. Ethylene is produced for a variety of uses in large quantities; about 47 billion pounds were produced in 1995 (Chemical and Engineering News 1996). Industrial release of ethylene to the air is substantial throughout the developed world. IARC (1994) reports an estimated total industrial release of 17,400 tons of ethylene in the United States in 1991. A report from the American Petroleum Institute (Suriano 2003) in support of the EPA Toxic Release Inventory indicates that 1.7 billion pounds of ethylene was released by petroleum refineries in 2000.

Volatilization of soil-borne ethylene is likely, based on the compound's high vapor pressure of 5.2×10^4 and a Henry's Law constant of 2.3×10^{-1} atm-m^3/mole at 25°C (HSDB 2001). As listed in Table 1, these and other physical-chemical characteristics also favor volatilization of ethylene from the surface of marine and freshwater systems. However, although sparingly soluble in water, the compound has been detected in oceans, lakes, and rivers in and around the United States. For example, concentrations of ethylene up to 35 nL/L were measured in water samples taken in the Mississippi delta.

Table 1. Summary of Physical-Chemical Properties of Ethylene

CAS No.	74-85-1
Molecular weight	28.05
Color	Colorless

Table 1. Summary of Physical-Chemical Properties of Ethylene

Physical state	Gas
Melting point	-169°C
Boiling point	-103.7°C
Odor	Sweet
Solubility	131 mg/L in water at 20-25 °C slightly soluble in benzene, ethanol, acetone, soluble in diethyl ether
Partition coefficients:	
Log K_{ow}	1.13
Log K_{oc}	2.0–2.5
Vapor pressure at 25 °C	5.2×10^4 mm Hg
Vapor Density	0.978 (air = 1)
Henry's Law constant at 25 °C	2.3×10^{-1} atm.m^3/mole
Conversion factors	1 ppm = 1.15 mg/m^3 1 mg/m^3 = 0.87 ppm

Sources: HSDB (2001), IARC (1994)

A number of mechanisms have been suggested for how the chemical is degraded in the environment. For example, the compound can degrade rapidly in the atmosphere as it reacts with photochemically-produced hydroxyl radicals. This process has a half-life of about 1.9 days. Nitrate radicals and ozone will also cause ethylene degradation, however at a lower rate. Ethylene can also be broken down as a result of microbial action as determined by pure culture research, however, it is expected to oxidize to ethylene oxide which is no metabolized further and may accumulate in the environment (HSDB 2001).

Given the volatility of ethylene, it is unlikely that it would persist in the environment long enough to allow for significant exposures to terrestrial wildlife. In the event that exposure would occur, the most likely route would be inhalation followed possibly by the dermal route. Importantly, ethylene is readily converted to ethylene oxide, which is somewhat more stable and could pose some risk to wildlife.

2.3 Summary of Mammalian Toxicity

2.3.1 Mammalian Toxicity - Oral

Given the gaseous nature of ethylene at ambient temperatures and pressures, there are no data on the toxicological effects of ethylene when administered via the oral route.

2.3.1.1 Studies Relevant for Mammalian TRV Development for Ingestion Exposures

Not applicable.

2.3.2 Mammalian Inhalation Toxicity

2.3.2.1 Mammalian Inhalation Toxicity – Acute

Due to the fact that ethylene serves as a rapid onset anesthetic, humans and animals have been exposed to relatively high concentrations without notable long-term adverse effects. For example, rats exposed to ethylene at concentrations of up to 500,000 ppm for 5 hours are reported to have suffered no long-term adverse effects (HSDB 2001). The apparent tolerance to high concentrations of ethylene in animals and humans has precluded the identification of a reliable compound-specific median lethal concentration (LC_{50}). However, it appears that concentrations of ethylene necessary to induce effective anesthesia come close to inducing hypoxia as the proportion of oxygen in the ethylene-air mixture is reduced.

Although there are few if any toxicological consequences of exposure to ethylene via inhalation, the ability of the compound to react with biological macromolecules has been demonstrated. For example, Eide et al. (1995) exposed male Sprague-Dawley rats to ethylene (one of a range of alkenes under investigation) at 300 ppm for 12 hours/day on three separate days. Exposure took place in a conically-shaped steel chamber with a glass door and walls. At termination, aliquots of blood and samples of lung, brain, liver, kidney, and peripheral fat were measured for ethylene. The formation of DNA adducts in liver and lymphocytes were monitored using the ^{32}P-postlabelling technique detected using gas chromatography/mass spectrometry. N-(2-hydroxyalkyl) valine adducts of hemoglobin and 7-alkylguanine adducts of DNA were detected consistently in these experiments, including N-(2-hydroxyethyl) valine and 7-ethylguanine when ethylene was used as the test compound.

2.3.2.2 Mammalian Inhalation Toxicity – Subchronic

An experiment by Vergnes and Pritts (1994) used a subacute dosing regime to examine ethylene's ability to induce the formation of micronuclei in the bone marrow of male F344 rats and B6C3F1 mice. Ten animals/group were exposed to 0, 40, 1000, and 3000 ppm ethylene, 6 hours/day, 5 days/week for 4 weeks, with bone marrow collected 24 hours after the last exposure. Exposure took place in a steel inhalation chamber with glass windows. Examination of cell smears revealed little if any formation of micronuclei or polychromatic nuclei in ethylene-exposed groups, although the incidence of these features was significantly increased in the cells of animals receiving 200 ppm ethylene oxide, a major carcinogenic metabolite of ethylene. This finding appears uncharacteristic in view of the likelihood that ethylene oxide is a metabolite of ethylene. However, the contradiction may have been explained by Walker et al. (2000) who used a similar experimental protocol to show that while both ethylene and ethylene oxide induce the formation of N-(2-hydroxyethyl) valine in hemoglobin and N7-(2-hydroxyethyl)guanine in DNA, only ethylene oxide had the ability to increase the frequency of

Hprt mutants in splenic T cells. The authors presented evidence to show that the cytochrome P4502E1-mediated conversion of ethylene to ethylene oxide saturates at levels that are insufficient to trigger the toxic responses that are typical of ethylene oxide exposure.

The Chemical Industry Institute of Toxicology (CIIT) has carried out two full-scale studies on the toxicology of ethylene, one of which was reported by Rhudy et al. (1978). The protocol featured the exposure of 15 "albino" rats/sex/group to 0, 300, 1000, 3000, or 10,000 ppm ethylene, 6 hours/day, 5 days/week for 13 weeks. Ethylene was delivered in unspecified inhalation chambers. During the study clinical signs, mortality, body weights, and food consumption were monitored daily; clinical chemistry, hematological, and urinalysis parameters were monitored in controls and high dose groups on days 6, 45 and 83; and full necropsies and histopathological evaluations were carried out on all survivors at termination. However, there were no compound-related differences in treatment groups compared to controls in any of the parameters under evaluation.

2.3.3.4 Mammalian Inhalation Toxicity – Chronic

The second CIIT study extended the duration to 24 months for 120 F344 rats/sex/group exposed to 0, 300, 1000, or 3000 ppm ethylene (Hamm et al. 1984). Exposure took place in four glass and stainless-steel chambers. Animals were euthanized on an interim basis after 6, 12, and 18 months, with these subjects and all survivors monitored for survival, clinical signs, ophthalmologic characteristics, hematology, clinical chemistry, and urinalysis. A full suite of histopathological examinations were carried out in control and high dose groups although, in these as in all other parameters under investigation, there appears to have been no compound-related effects.

2.3.3.5 Studies Relevant for Mammalian TRV Development for Inhalation Exposures

The use of high concentrations of ethylene as an anesthetic, with full recovery of faculties on cessation of exposure, is consistent with the negative toxicological results outlined in Sections 2.3.3.1–2.3.3.4. Taken together, these findings point to the benign nature of the compound in biological systems and argue against the likelihood that a viable TRV for ethylene can emerge from the overall toxicological information on the compound. However, the formation of 2-hydroxyethyl derivatives of hemoglobin and guanine shows that ethylene has biochemical activity, most likely mediated through its ethylene oxide intermediate. The disparity between the benign effects of ethylene and the more severe effects of ethylene oxide in toxicological tests has been addressed by Walker et al. (2000) and in a review by Bolt (1998) who estimated that exposure concentrations of 1000 ppm ethylene would be equivalent to about 7.5 ppm ethylene oxide. By implication, this concentration would probably be below the threshold at which any toxicological impacts (of ethylene oxide) would become apparent.

2.3.4 Mammalian Inhalation Toxicity – Other

Aveyard and Collins (1997) used Organization for Economic Cooperation and Development (OECD) guideline 421 to test the effects of ethylene on fertility, pregnancy, maternal and suckling behavior, and F1 growth and development in rats (strain unstated) exposed to ethylene. They reported that 10 parental animals/group were exposed head only to 0, 200, 1000, or 5000 ppm ethylene, 6 hours/day from 2 weeks prior to mating until gestation day (GD) 20 (males) or day 4 post-partum (females). No animals died during treatment, and no compound-related effects were evident on weight gain, food consumption, fertility, fecundity, litter characteristics, or on pathology or histopathology in either generation.

2.3.5 Mammalian Dermal Toxicity

No data are available.

2.4 Summary of Avian Toxicology

No toxicological data for the effects of ethylene on avian species was located. Ecotoxicological research on the effects of this compound on birds is recommended.

2.5 Amphibian Toxicology

No toxicological data for the effects of ethylene on amphibian species was located. Ecotoxicological research on the effects of this compound on amphibians is recommended.

2.6 Reptilian Toxicology

No toxicological data for the effects of ethylene on reptiles was located. Ecotoxicological research on the effects of this compound on reptiles is recommended.

3. RECOMMENDED TOXICITY REFERENCE VALUES

3.1 Toxicity Reference Values for Mammals

3.1.1 TRVs for Ingestion Exposures for the Class Mammalia

At this time it is not possible to derive a TRV for oral route of exposure for ethylene due to the lack of toxicity data and the gaseous nature of the compound which renders an oral exposure unlikely.

3.1.2 TRVs for Inhalation Exposures for the Class Mammalia

With the use of ethylene in high concentrations as an anesthetic, there is no evidence of toxicological effects occurring at levels that would be likely in the environment. It is, however, evident

that there are toxicological effects through its ethylene oxide intermediate. However, the effects were molecular in nature and were not linked to more toxicologically relevant endpoints such as tumor formation, morbidity or death. As a result, a TRV could not be derived for ethylene at this time.

4. IMPORTANT RESEARCH NEEDS

The limited availability of data on the toxicity of ethylene to wildlife species precludes the development of a TRV. Hence, more studies of the compound and its derivatives are recommended. The toxicity and biochemical activity of ethylene and ethylene oxide warrant attention to explain the relationship between these compounds. Also, chronic toxicity studies on non-mammalian wildlife such as birds, reptiles and amphibians are particularly warranted.

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APPENDIX A

LITERATURE REVIEW

Separate searches in DIALOG (three in all) were carried out on ethylene on April 20, 2001, and on May 2, 2001.

In the first search the following files were scanned:

File 155 MEDLINE, File 156 TOXLINE, File 5 BIOSIS, File 10 AGRICOLA, File 203 AGRIS, File 399 Chemical Abstracts, File 77 Conference Papers Index, File 35 Dissertation Abstracts, File 40 ENVIRONLINE, File 68 Environmental Bibliography, File 76 Life Sciences Collection, File 41 Pollution Abstracts, File 185 Zoological Record, File 6 NTIS, File 50 CAB, File 144 PASCAL, File 34 SCISEARCH, and File 434 SCISEARCH.

The search strategy for **Amphibians & Reptiles**:

- Chemical name, CAS numbers
- AND (amphibi? or frog or frogs or salamander? or newt or newts or toad? or reptil? or crocodil? or alligator? or caiman? snake? or lizard? or turtle? or tortoise? or terrapin?)
- AND (reproduc? or diet or dietary or systemic or development? or histolog? or growth or neurological or behav? or mortal? or lethal? or surviv? or (drinking()water))
- NOT glycol
- RD (reduce duplicates)
- NOT dibromide
- NOT dichloride
- NOT (human? or culture? or subcutaneous or vitro or gene or inject? or tumo? or inhalation or carcin? or cancer?)

The search strategy for **Birds:**

- Chemical name, CAS numbers
- AND chicken? or duck or duckling? or ducks or mallard? or quail? or (japanese()quail?) or coturnix or (gallus()domesticus) or platyrhyn? or anas or aves or avian or bird? or (song()bird?) or bobwhite? or (water()bird) or (water()fowl)
- AND (reproduc? or diet or dietary or systemic or development? or histolog? or growth or neurological or behav? or mortal? or lethal? or surviv? or (drinking()water))

- NOT (human? or culture? or subcutaneous or vitro or gene or inject? or tumo? or inhalation or carcin? or cancer?)
- RD (reduce duplicates)
- NOT dibromide or dichloride
- NOT dibromide
- NOT dichloride

The search strategy for **Laboratory Mammals:**

- Chemical name, CAS numbers
- AND (rat or rats or mice or mouse or hamster? or (guinea()pig?) or rabbit? or monkey?)
- AND (reproduc? or diet or dietary or systemic or development? or histolog? or growth or neurological or behav? or mortal? or lethal? or surviv? or (drinking()water))
- NOT (human? or culture? or subcutaneous or vitro or gene or inject? or tumo? or inhalation or carcin? or cancer?)/ti,de
- NOT (meeting()poster)
- NOT (meeting()abstract)
- NOT (conference()proceeding?)
- RD (reduce duplicates)
- NOT (patient? or cohort? or worker? or child? or infant? or women or men or occupational)
- NOT (glycols or polymer or poly or tetraacetic or tetraacetate or dichlorides)
- NOT EDTA
- NOT (dimethanesulphonate? or dimethanesulfonate? or diamine? or EDS)
- AND LA=English

The search strategy for **Wild Mammals:**

- Chemical name, CAS numbers
- And (didelphidae or opossum? or soricidae or shrew? Or talpidae or armadillo? or dasypodidae or ochotonidae or leporidae) or canidae or ursidae or procyonidae or mustelidae or felidae or cat or cats or dog or dogs or bear or bears or weasel? or skunk? or marten or martens or badger? or ferret? or

mink? Or aplodontidae or beaver? or sciuridae or geomyidae or heteromyidae or castoridae or equidae or suidae or dicotylidae or cervidae or antilocapridae or bovidae arvicolinae or mycocastoridae or dipodidae or erethizontidae or sigmodon? or (harvest()mice) or (harvest()mouse) or microtus or peromyscus or reithrodontomys or onychomys or vole or voles or lemming?

- AND (reproduc? or diet or dietary or systemic or development? or histolog? or growth or neurological or behav? or mortal? or lethal? or surviv? or (drinking()water))
- NOT (human? or culture? or subcutaneous or vitro or gene or inject? or tumo? or inhalation or carcin? or cancer?)/ti,de
- NOT (meeting()poster?)
- NOT (meeting()abstract?)
- NOT (conference()proceedings?)
- NOT (patient? or cohort? or worker? or child? or infant? or women? or men? or occupational?)
- RD (reduce duplicates)
- NOT steriliz?
- NOT oxide

When the search retrieved an appreciable number of hits, *keywords in context* were reviewed to minimize costs before any abstracts were downloaded (Tier 1). However, when only a limited number of studies were identified by the search, the abstracts were downloaded at the time of the search (Tier 2).

The second search examined the same files as the first but used the following structure:

For **Laboratory Animals**

- CAS Number
- AND (rat or rats or mice or mouse or hamster? or (guinea()pig?) or rabbit? or monkey?)
- AND (reproduc? or diet or dietary or systemic or development? or histolog? or growth or neurological or behav? or mortal? or lethal? or surviv? or (drinking()water))
- RD (reduce duplicates)

The third search examined the following databases

File 155 Medline, File 156 Toxline, File 535 Thomas Register Online, File 76 Life Sciences Collection, File 185 Zoological Record Online, File 5 Biosis Reviews.

For **Birds**

- CAS Number

- AND (chicken? or duck or duckling? or ducks or mallard? or quail? or (japanese()quail?) or coturnix or (gallus()domesticus) or platyrhyn? or anas or aves or avian or bird? or (song()bird?) or bobwhite? or (water()bird) or (water()fowl))

- RD (Reduce Duplicates)

For **Wild Mammals**

- CAS Number

- AND (didelphidae or opossum? or soricidae or shrew? Or talpidae or armadillo? or dasypodidae or ochotonidae or leporidae) or canidae or ursidae or procyonidae or mustelidae or felidae or cat or cats or dog or dogs or bear or bears or weasel? or skunk? or marten or martens or badger? or ferret? or mink? Or aplodontidae or beaver? or sciuridae or geomyidae or heteromyidae or castoridae or equidae or suidae or dicotylidae or cervidae or antilocapridae or bovidae arvicolinae or mycocastoridae or dipodidae or erethizontidae or sigmodon? or (harvest()mice) or (harvest()mouse) or microtus or peromyscus or reithrodontomys or onychomys or vole or voles or lemming?)

- RD (Reduce Duplicates)

For **Amphibians/Reptiles**

- CAS. Number

- AND (amphibi? or frog or frogs or salamander? or newt or newts or toad? or reptil? or crocodil? or alligator? or caiman? snake? or lizard? or turtle? or tortoise? or terrapin?)

- RD (reduce duplicates)

As noted in Section 2.1, 538 hits on ethylene were obtained in the initial searches, of which 9 were selected for retrieval.

資料　１３

国立労働生活研究所：スウェーデン労働基準の科学的基礎 13.
（抜粋）エチレンのコンセンサス・レポート
１９９６年１２月

National Institute for Working Life
December 11, 1996

Scientific Basis for Swedish Occupational Standards

XVIII

Consensus Report for Ethene

Consensus Report for Ethene

December 11, 1996

Physical and chemical data. Occurrence

CAS No:	74-85-1
Systematic name:	ethylene
Synonyms:	acetene, elayl, olefiant gas
Formula:	$CH_2=CH_2$
Molecular weight:	28.05
Density:	0.98 (air = 1)
Boiling point:	- 104 °C
Vapor pressure:	4270 kPa (0 °C)
Melting point:	- 169 °C
Explosion threshold:	2.75 vol % in air (100 kPa; 20 °C)
Distribution coefficient:	log P_{OW} = 1.13 (octanol/water)
Conversion factors:	1 ppm = 1.15 mg/m^3
	1 mg/m^3 = 0.87 ppm

Ethene at room temperature is a colorless gas with a sweet odor and taste. The reported odor threshold is 290 ppm (333.5 mg/m^3) (1, 26). The gas dissolves readily in water, acetone, ethanol and benzene. Ethene is stable under normal pressure and temperature conditions, but may polymerize at higher pressure and temperature.

Ethene is used primarily in the production of polyethylene and ethylene oxide / ethylene glycol. It is also used as a raw material in the production of other chemical substances. Ethene is used to accelerate the ripening of fruit. (It is formed naturally by ripening fruit.)

There are virtually no data on occupational exposure to ethene in connection with production of the substance. It is usually produced in closed systems. In one study (17) it is estimated that during the years 1941 to 1947 the exposure level for ethene around production of ethylene oxide was about 600 mg/m^3. Measurements of occupational exposure to ethene in warehouses where the gas is used to control the ripening of bananas showed air concentrations ranging from 0.02 to 3.85 mg/m^3, with a mean value of 0.35 mg/m^3 (28). In a study of firemen, it was found that they were exposed to ethene in some phases of fighting fires (20).

Uptake, biotransformation, excretion

Six volunteers were exposed to 0, 5 or 50 ppm ethene (0, 5.75 or 57.5 mg/m^3) for two hours. Most (94.4%) of the inhaled ethene was immediately exhaled. Calculations based on clearance of uptake and metabolic clearance indicated that alveolar retention at steady state was 2% and the biological half time was 0.65 hours (12). From theoretical calculations of gas uptake in the lungs, it can be concluded that the low uptake of ethene is due to its low solubility in blood.

Ethene can be detected in exhaled air of unexposed persons. Women exhale more ethene at the time of ovulation. The biochemical origin of this endogenously produced ethene has not been explained, but four theories have been proposed: lipid peroxidation, enzyme-catalyzed oxidative breakdown of methionine, oxidation of hemoglobin, and metabolism in intestinal bacteria (18).

Two hemoglobin adducts, N-(2-hydroxyethyl)histidine (HOEtHis) and N-(2-hydroxyethyl)valine (HOEtVal), have been used as dose measures for formation of ethylene oxide from ethene.

Exposure to ethene at concentrations of 10 to 20 ppb (11.5 to 23 μg/m^3) has been associated with an increase of adducts (HOEtVal) amounting to 4 – 8 pmol/g Hb at steady state (29). Fruit store workers exposed to 0.02 to 3.35 ppm ethene (0.023 to 3.85 mg/m^3) had adduct (HOEtVal) levels of 22 to 65 pmol/g Hb; levels in unexposed controls were 12 to 27 pmol/g Hb (28). The adduct level due to endogenous ethylene alone is estimated to be about 12 pmol/g Hb (12).

It has been estimated from adduct data that about 2 to 3% of inhaled ethene is metabolized to ethylene oxide (14, 28). Exposure to 1 ppm ethene (1.15 mg/m^3) for 40 hours/week is calculated to increase the adduct level by 100 to 120 pmol/g Hb (9).

Mice were exposed to 17 ppm (22.3 mg/m^3) ^{14}C-labeled ethene for one hour. Four hours later radioactivity was found primarily in kidneys and liver, with lesser amounts in testes and brain. A 48-hour urine sample contained S-(2-hydroxyethyl)cysteine, indicating that the ethene had been metabolized to ethylene oxide (8). Fischer-344 rats that were exposed to 10,000 ppm (11,500 mg/m^3) radioactively labeled ethene for 5 hours eliminated most of the radioactivity as exhaled ethene, while smaller amounts were excreted in urine and feces or exhaled as CO_2. Minor amounts of radioactivity were found in blood, liver, intestines and kidneys. The amounts of radioactivity in urine and CO_2 were higher in animals that had been pre-treated with Aroclor (a commercial PCB mixture), which indicates that ethene metabolism can be stimulated by substances that induce the mixed function oxidase system (15).

When Sprague-Dawley rats were exposed to between 0.1 and 80 ppm (0.12 and 92 mg/m^3) ethene, they eliminated 24% of available ethene by biotransformation and 76% by exhalation of unchanged ethene. The alveolar retention at steady state was 3.5% and the biological half time was 4.7 minutes (12). Metabolism was saturated at concentrations above 80 ppm (92 mg/m^3), with a maximum metabolism rate (V_{max}) of 0.24 mg/hour x kg body weight (11).

When Sprague-Dawley rats were exposed for 21 hours to ethene levels exceeding 1000 ppm (1150 mg/m^3) the amount of ethene absorbed per unit of time was constant (2). When Fischer-344 rats were exposed to 600 ppm (690 mg/m^3) ethene, the blood level of ethylene oxide rose rapidly during the first five to ten minutes and then dropped to a level that remained constant during the remainder of the 60-minute exposure. The level of cytochrome P-450 in liver declined steadily during the experiment (22). This was taken to indicate that during metabolism of ethene the phenobarbital-induced form of cytochrome P-450 is destroyed by transformation of the cytochrome heme to an abnormal porphyrin (23).

Sprague-Dawley rats were exposed to 300 ppm (345 mg/m^3) ethene 12 hours/day for three consecutive days: the concentration of ethene was low in all examined organs 12 hours after the last exposure. However, the levels of hemoglobin adducts and of 7-alkylguanine in lymphocytes and liver were elevated, indicating the formation of ethylene oxide (10).

Hemoglobin adduct (HOEtVal) levels of about 100 pmol/g Hb have been measured in several strains of rats, mice and hamsters after exposure to ethene (18). Calculations based on animal data indicate that uptake of 1 mg ethene per kg body weight corresponds to a tissue dose of ethylene oxide amounting to 0.03 mg x hour/kg body weight. This value agrees with the one calculated for human uptake (32).

Toxic effects

Ethene is not irritating to eyes or skin (4). People exposed to a concentration of 37.5% in air for 15 minutes experienced some memory disturbance, and 50% in air results in loss of consciousness due to oxygen deprivation (4).

Mice repeatedly exposed to concentrations resulting in loss of consciousness showed no histopathological changes in kidneys, adrenal glands, heart or lungs (24). The concentration was described as ”atmosphere in which the partial pressure of oxygen was 20 per cent and ethylene 90 per cent.”

Fischer-344 rats exposed to 10,000 ppm (11,500 mg/m^3) ethene for 5 hours showed no toxic effects (15). Nor were toxic effects observed in Sprague-Dawley rats with ethene exposures up to 10,000 ppm (11,500 mg/m^3) 6 hours/day, 5 days/week in a 90-day study (25), or in Fischer-344 rats with exposures up to 3000 ppm (3450 mg/m^3) in a two-year study (16). This absence of toxicity may be due to saturation of ethene metabolism (18).

Rats pre-treated with Aroclor and 24 hours later exposed to ethene concentrations of 10,000, 30,000 or 57,000 ppm (11,500, 34,500 or 65,550 mg/m^3) for 4 hours had dose-dependent effects on liver, indicated by elevated serum levels of sorbitol dehydrogenase and alanin-α-ketoglutarate transaminase and by the histological observation of centrilobular necrosis (5, 6, 15).

Mutagenicity, carcinogenicity, teratogenicity

Ethene caused no mutations in tests with *Salmonella typhimurium* (TA 100), either with or without metabolic activation (34). Ethene induced no micronuclei in the bone marrow of

rats and mice exposed to up to 3000 ppm (3450 mg/m^3) 6 hours/day, 5 days/week for four weeks (33).

The DNA adduct 7-(2-hydroxyethyl)guanine (7-HOEtGua) was found in levels of 2 to 6 nmol/g DNA in lymphocytes from untreated Sprague-Dawley rats (13) and in DNA from several different tissues from Fischer-344 rats and B6C3F1 mice (35). After mice were exposed for eight hours to 11 ppm (12.9 mg/m^3) radioactively labeled ethene, 7-alkylation of guanine could be demonstrated in DNA from liver, spleen and testes: 0.17 nmol/g DNA was measured in liver; 0.098 in spleen and 0.068 nmol/g DNA in testes, which was less that 10% above the background level (27).

Groups of Fischer-344 rats (120 of each sex) were exposed to 0, 300, 1000 or 3000 ppm (0, 345, 1150 or 3450 mg/m^3) ethene 6 hours/day, 5 days/week for up to 24 months. Rats were sacrificed and examined after 6, 12, 18 and 24 months. There was no difference in survival between exposed rats and controls. Histological comparisons of the high-dose group and the controls revealed no indications of any exposure-related toxicity and no elevated incidence of tumors (16).

Groups of Sprague-Dawley rats (both sexes) were exposed to 0 or 10,000 ppm ethene (0 or 11,500 mg/m^3) 8 hours/day, 5 days/week for three weeks. One week later the animals were given polychlorinated biphenyls (unspecified), 10 mg/kg body weight, by gavage twice a week for 8 weeks. The animals were then sacrificed and examined for ”ATPase-deficient foci.” There was no difference between the ethene-exposed animals and controls. (When ethylene oxide was used as a positive control, there was a pronounced increase of foci.) (7)

According to the IARC (18), it is not possible to determine whether ethene is carcinogenic to either man or experimental animals (”inadequate evidence”) and ethene has therefore been placed in Group 3: ”unclassifiable as to its carcinogenicity to humans.” As for the metabolite ethylene oxide, in the judgement of the IARC (19) there is ”limited evidence” that it is carcinogenic to humans and ”sufficient evidence” that it is carcinogenic to experimental animals, and in the overall assessment ethylene oxide is therefore placed in Group 1: ”carcinogenic to humans.”

In a theoretical presentation (29, 30, 31) it is postulated that ethene might cause cancer via activation to ethylene oxide which then binds to DNA, and that the consequent risk of cancer in Sweden due to ethene in city air would be equivalent to 30 cases per year (at an average exposure of 1.8 mg/m^3).

One study reports 6 miscarriages among 15 pregnant women who were working in a petrochemical industry. This rate was higher than that for 1,549 women who were living in the surrounding area. The main product was ethene (350,000 tons/year), but the women were also exposed to other substances including ethylene oxide, vinyl chloride and phthalates. No exposure data are given, but measured ethene concentrations in air outside the plant were on average 10 to 15 ppb (2).

Dose-response / dose-effect relationships

There are no data that can be used as a basis for calculating a dose-effect or dose-response relationship for human exposure to ethene. Occupational exposures of 0.023 to 3.5 mg/m^3 have resulted in elevated formation of hemoglobin adducts (28). Data from animal studies are summarized in Table 1.

Table 1. Effects of ethene inhalation on experimental animals.

mg/m^3	Duration	Species	Effects	Ref.
12.9	8 hours	Mouse	7-alkylation of guanine in DNA	27
92	6 hours	Rat	Saturation of ethene metabolism	11
3450	28 days	Mouse	No increase in micronuclei	33
3450	2 years	Rat	No toxic effects	16
11,500	5 hours	Rat	No toxic effects	15
11,500	90 days	Rat	No toxic effects	25
11,500	24 hours	Rat (pre-treated with Aroclor)	Liver effects	5, 6

Conclusions

Judging from available data on toxicity to humans, the critical effect of exposure to ethene is its effect on the central nervous system. (Ethene has been used as an anesthetic.) From animal data it can be observed that, if the animals have been enzyme-induced, effects on the liver may be the critical ones.

It has been debated whether exposure to ethene can give rise to toxic effects and/or cancer caused by the metabolite ethylene oxide. In its 1981 report, the Criteria Group stated that the critical effects of exposure to ethylene oxide were the mutagenic, cytogenetic and carcinogenic effects, and that cytogenetic effects of ethylene oxide were seen at occupational exposures of about 2 mg/m^3 (21).

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資料　１４

馬鈴しょ萌芽抑制効果に対するエチレン濃度限界に関する試験

（平成 20 年秋～21 年夏、酪農学園大学）

１．目的

加工用馬鈴しょの貯蔵中の萌芽を抑制し、国産馬鈴しょの周年供給体制を確立することを目的とし、エチレンによる芽の生長抑制効果と加工適性維持のための限界エチレン処理濃度を求めるために、代表的な 2 品種を用いて貯蔵試験を行った。

２．試験方法

１）供試材料

平成 20 年、帯広市川西産「きたひめ」、「スノーデン」を用いた。

２）エチレンの供給方法および濃度

ガス置換デシケータを利用したエチレン供給貯蔵基礎実験装置（参考資料１）を用いて 10 月 28 日から貯蔵試験を開始した。

３）貯蔵方法

無処理区も同様の貯蔵容器（デシケータ）を用いた（参考資料１を参照）。

貯蔵温度は 8℃とし、エチレン濃度はこれまでの試験において 4ppm で十分な効果が得られることが明らかになっているため、その 5 倍濃度の処理区として 20ppm と設定し、無処理区として 0ppm 区を設定した。

４)測定項目

貯蔵環境の温度、湿度、エチレン濃度については、貯蔵期間中継続して測定した。品質については、10月28日、12月26日、2月16日、3月20日、4月24日、5月29日、7月3日に測定した。

(1)恒温室内温湿度

恒温室内温度、湿度をデーターロガーを用いて測定した。

(2)貯蔵容器（デシケータ）内エチレン濃度、二酸化炭素濃度

ガスタイトシリンジにより貯蔵容器の上下2箇所から容器内ガスを採取し、ガスクロマトグラフを用いてエチレン濃度および二酸化炭素濃度を測定した。

(3)試料質量、水分含量

電子天秤を用いて試料質量を測定し、質量減少率を求めた。水分含量は70℃24時間恒温乾燥法により求めた。

(4)芽の長さ

5㎜以下、5㎜以上の芽の塊茎当たりの個数、塊茎毎の最長芽の長さ、塊茎当たりの芽の質量を測定した。

(5)糖含量

HPLCを用いてショ糖、ブドウ糖、果糖含量を測定した。

(6)硬度

レオメータを用い、直径2㎜の円筒状プランジャを50㎜/sの速度で貫入させて荷重を測定した。

(7)ポテトチップカラー

試料を約1㎜の厚さにスライスし、180℃のサラダオイルで約120秒間フライし、その色をアグトロンメーターを用いて測定した。

３．結果

図 1～2 に貯蔵中エチレン濃度の推移を示す。

「きたひめ」「スノーデン」の初期のエチレン処理区において、急激な濃度の上昇があったが、これはコンプレッサの不調により空気の供給が停止したためである。また、このとき無処理区においてもエチレンが一時的に検出された。これ以外ではいずれもほぼ設定どおりに制御することができた。貯蔵開始当初は 1 時間換気、5 時間休止のサイクルで換気及びエチレンの供給を行っていたが、特に、エチレン区において CO_2 濃度の上昇が見られたため、2 時間換気、4 時間換気に変更することにより CO_2 濃度は 0.1%以下に抑えることができ、以後このサイクルで行った。

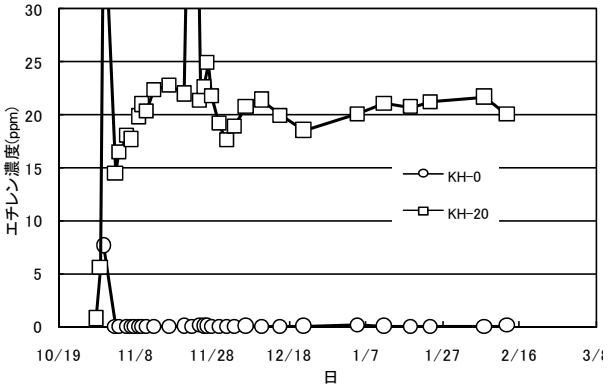

図1 貯蔵中エチレン濃度の推移(きたひめ)

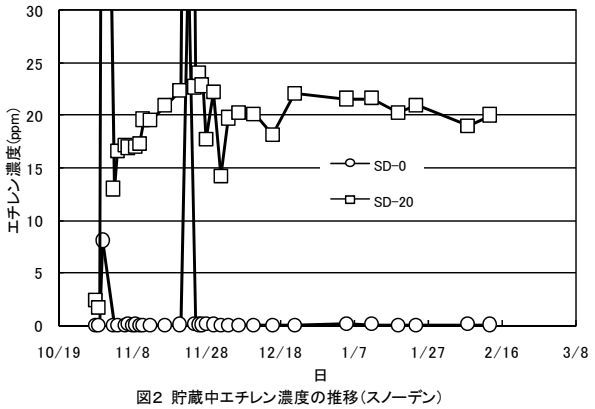

図2 貯蔵中エチレン濃度の推移(スノーデン)

図 3～4 に、塊茎毎の最長芽の長さの平均値の推移を示す。

いずれの品種においても 2 月 16 日の時点で萌芽が見られ、特に、無処理区において芽の伸長が大きかった。

貯蔵終了時点でいずれの品種においてもエチレン処理区では芽の長さが 20㎜ 以下に抑制された。

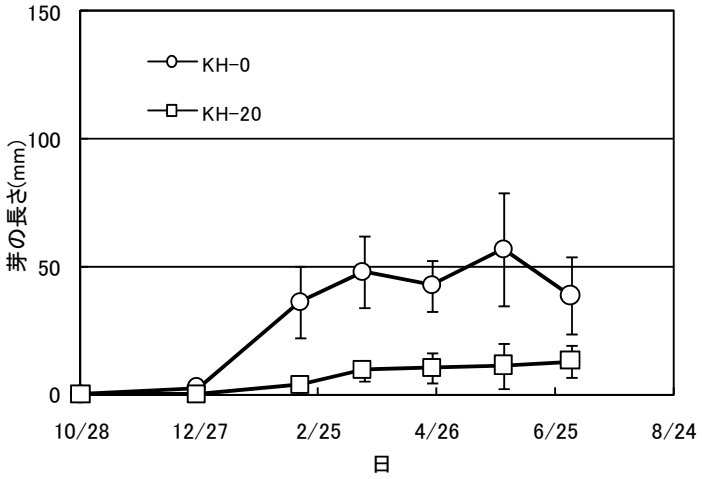

図3 最長芽の長さの推移(きたひめ)

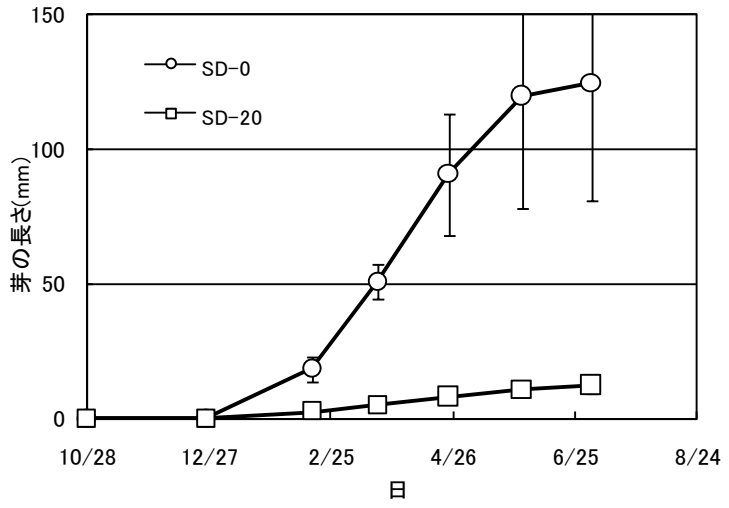

図4 最長芽の長さの推移(スノーデン)

図 5～6 に、還元糖含量の推移を示す。

いずれの品種も貯蔵初期に還元糖が増加し、その後低下する傾向にあり、貯蔵末期に再び増加する傾向もみられた。

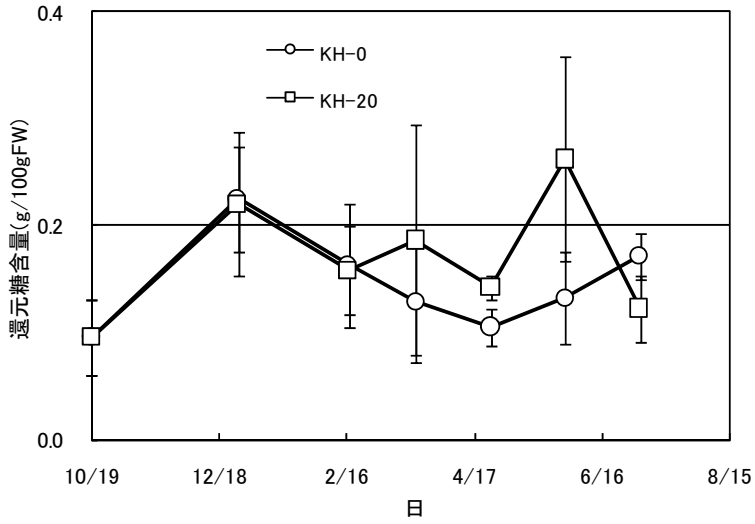

図5 還元糖含量の推移(きたひめ)

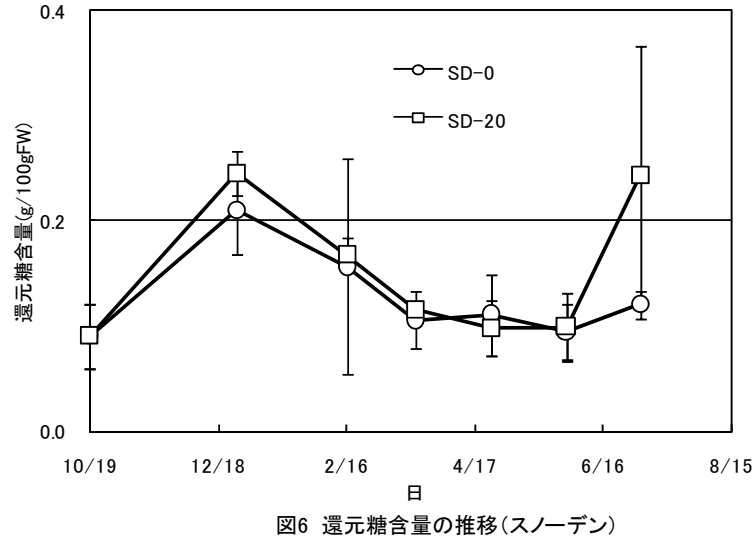

図6 還元糖含量の推移(スノーデン)

図 7～8 に、ポテトチップカラーの推移を示す。

還元糖含量の推移を反映し、貯蔵初期にポテトチップカラーが低下し、その後回復する傾向にあるが、「きたひめ」は低下の度合いが小さい。

また、貯蔵末期に低下する傾向にあった。いずれも 20ppm のエチレン処理においてもポテトチップカラーの大きな低下はなく、5 月下旬頃までは原料としての利用に耐える加工適性を保っていた。

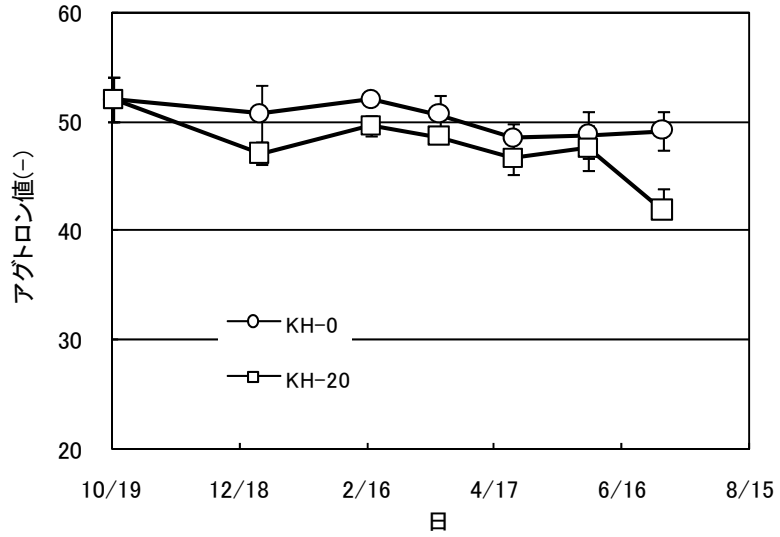

図7 チップカラーの推移(きたひめ)

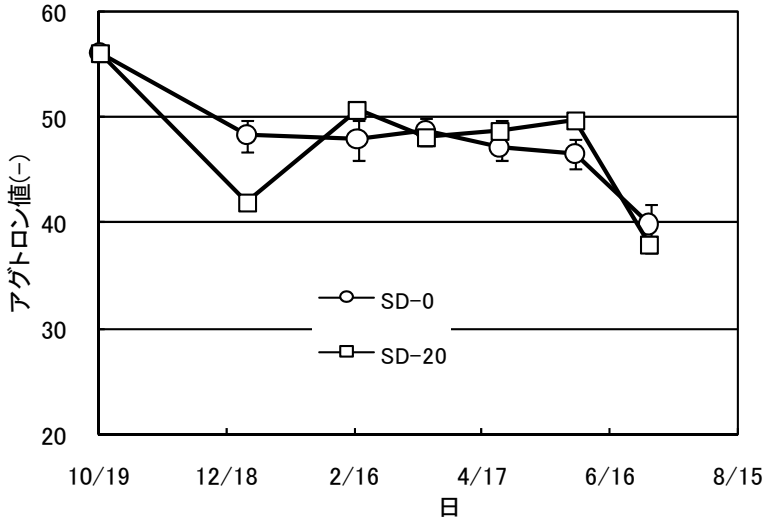

図8 チップカラーの推移(スノーデン)

４．要　約

エチレンによる芽の生長抑制効果と加工適性維持のための限界エチレン処理濃度を求めるために代表的な 2 品種を用いて貯蔵試験を行った。

エチレン濃度 20ppm で貯蔵を行った場合においても、芽の伸長は抑えられ、ポテトチップカラーの顕著な低下はなかった。

資料　１５

エチレン処理による馬鈴しょの残留性に関する試験

（平成 20 年秋～21 年夏、酪農学園大学、十勝農業試験場）

１．目　的

エチレン処理した馬鈴しょの中のエチレン残留量が通常の食品中に含まれるエチレン量を超えることがないこと等を裏付けるために、エチレン処理した馬鈴しょの長期貯蔵後のエチレン処理区と無処理区の塊茎中のエチレン濃度を調査する。

２．試験方法

○.酪農学園大学

１）供試品種：「きたひめ」、「スノーデン」、「トヨシロ」

２）試験期間：平成 20 年秋～21 年夏

３）エチレン：無処理区 0ppm、処理区は 4ppm、20ppm

４）試験実施：4 月 24 日、5 月 30 日

５）その他は参考試料 2 に示す。

○JA 士幌町（試験実施、試験担当は十勝農業試験場）

１）供試品種：「きたひめ」、「スノーデン」、「トヨシロ」

２）試験期間：平成 20 年秋～21 年夏

３）エチレン：無処理区 0ppm、処理区は 8ppm

４）試験実施：4 月 23 日、6 月 25 日

５）その他は参考資料 3 に示す。

○カルビーポテト（株）（参考）

１）供試品種：「スノーデン」

２）試験期間：平成 20 年秋～21 年夏

３）エチレン：無処理 0ppm、処理区 4ppm

４）試験実施：4 月 20 日

５）その他は種略

３．エチレン濃度の分析方法

酪農学園大学および JA 士幌町（十勝農試）でエチレン処理した馬鈴しょ 2 塊茎とスペーサーをラミネートフィルム袋に入れてヒートシールして密閉した（写真 1)。

フィルムにゴムパッチを貼付し注射針を刺し、真空ポンプにて内部の空気を完全に排気し（写真 2､3)、馬鈴しょ重量 300g に対し 1,000mL の空気を再度入れて封入した（写真 4)。

封入後、24 時間経過した時点（写真 5）で内部の空気をガスタイトシリンジでサンプリングしてガスクロマトグラフ（写真 6）にてエチレン濃度を測定した。

写真１．ビニールパック

写真 2．真空ポンプによる脱気

写真 3.真空状態

写真 4．一定量の空気を入れる

写真 5．空気を入れて 24 時間保管

写真 6．ガスクロ

４．結　果

表 1 に示す。

酪農学園大学において処理した馬鈴しょは、芽をすべて取り除いたのちに残留性試験を行ったが、その他の機関において処理したものについては、芽が付いたままの状態で試験に供試した。

酪農学園大学において処理した馬鈴しょでは、4 月 24 日の「きたひめ」20ppm 処理区においてのみエチレンが検出された。

JA 士幌町において処理した馬鈴しょでは、4 月 23 日の試料では無処理区においてのみエチレンが検出された。6 月 25 日においては、「トヨシロ」の無処理区を除いてエチレンが検出されたが、その他は無処理区の方が濃度が高かった。

カルビーポテト（株）において処理した馬鈴しょは、いずれもエチレンは検出されなかった。

本試験に用いた方法では、内生エチレンと処理に使用したエチレンの区別は出来ないが、ほとんどの場合エチレンが検出されないか、検出されても無処理区より濃度は低く、残留性は無いと判断できる。

表１　エチレン残留性試験結果

処理機関	試験期日	出庫後時間	品種	処理条件	質量 g	空気量 mL	エチレン濃度 ppm
酪農学園	4月24日	5時間後	きたひめ	0ppm	327.6	1092	-
				4ppm	304.4	1015	-
				20ppm	441.5	1472	0.084
			スノーデン	0ppm	309.9	1033	-
				4ppm	347.6	1159	-
				20ppm	315.8	1053	-
			トヨシロ	0ppm	308.3	1028	-
				4ppm	322.3	1074	-
酪農学園	5月30日	24時間後	きたひめ	0ppm	335.2	1117	-
				4ppm	318.9	1063	-
				20ppm	315.7	1052	-
			スノーデン	0ppm	372.6	1242	-
				4ppm	347.9	1160	-
				20ppm	402.1	1340	-
			トヨシロ	0ppm	330.8	1103	-
				4ppm	281.6	939	-

処理機関	試験期日	出庫後時間	品種	処理条件	質量 g	空気量 mL	エチレン濃度 ppm
士幌農協	4月23日	22時間後	きたひめ	0ppm	316.4	1055	0.094
				8ppm	222.2	741	-
			スノーデン	0ppm	365.5	1218	0.044
				8ppm	257.2	857	-
			トヨシロ	0ppm	313.9	1046	0.075
				8ppm	315.7	1052	-
士幌農協	6月25日	22時間後	きたひめ	0ppm	228.3	761	0.0897
				8ppm	250.4	835	0.0547
			スノーデン	0ppm	274.7	916	0.4877
				8ppm	255.6	852	0.0432
			トヨシロ	0ppm	269.4	898	-
				8ppm	243.1	810	0.0759

処理機関	試験期日	出庫後時間	品種	処理条件	質量 g	空気量 mL	エチレン濃度 ppm
カルビーポテト	4月28日	20時間後	スノーデン	0ppm	300.0	1000	-
				0ppm	318.8	1063	-
				0ppm	350.4	1168	-
				4ppm	313.1	1044	-
				4ppm	322.3	1074	-
				4ppm	335.0	1117	-