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LIFESPAN ORAL TOXICITY STUDY OF VINYL CHLORIDE IN RATS*

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Abstract—A lifespan oral toxicity study of vinyl chloride monomer (VCM) was carried out in Wistar rats, using five groups each of 60–80 males and 60–80 females. VCM was administered by incorporating polyvinyl chloride (PVC) powder with a high VCM content into the diet or by gastric intubation of a 10% VCM solution in soya-bean oil. The VCM doses (actual exposures) were 0 (control), 1·7, 5·0 and 14·1 mg/kg body weight day provided by diets containing PVC powder, and 300 mg/kg body weight given by stomach tube as a solution of VCM in oil on 5 days/wk. The death rate was higher in all VCM-treated groups than in the controls and increased with increasing VCM doses. The 14·1- and 300-mg/kg treatments were associated with shortened blood-clotting times, slightly increased α-foetoprotein levels in the blood serum, liver enlargement and an increased haematopoietic activity in the spleen. A variety of neoplastic and non-neoplastic treatment-related liver lesions was found at each of the VCM levels. The changes varied from swollen and irregularly-shaped mitochondria in hepatocytes to hepatocellular carcinomas and hepatic angiosarcomas. The tumour response of the liver appeared to shift from a predominance of angiosarcomas at the highest dose level via a mixture of angiosarcomas and hepatocellular tumours at the intermediate levels to the exclusive development of hepatocellular tumours at the lowest VCM level. Tumours attributable to VCM exposure and found at other sites included pulmonary angiosarcomas, extrahepatic abdominal angiosarcomas and tumours of the Zymbal glands; these neoplasms occurred at VCM levels of 5·0 mg/kg and above. In addition, there was some evidence that VCM exposure enhanced the development of abdominal mesotheliomas and of adenocarcinomas of the mammary glands. Thus, the present study showed that orally administered VCM is a carcinogen in rats, and that the "no-observed-adverse-effect level" in rats was lower than 1·7 mg/kg body weight/day under the rigorous conditions of continuous oral VCM exposure resulting from the release of VCM from PVC powder present in the gastro-intestinal tract.

INTRODUCTION

Industrial exposure to vinyl chloride monomer (VCM) has been associated with disorders such as acro-osteolysis, non-malignant liver disease, angiosarcoma and carcinoma of the liver, and tumours of the brain and lungs and of the lymphatic and haematopoietic systems (Haley, 1975; Hopkins, 1980; Monson, Peters & Johnson, 1974; Rawls, 1980; Thomas & Popper, 1975; Vale, Kipling & Walker, 1976; Waxweiler, Stringer, Wagoner, Jones, Falk & Carter, 1976). In addition, various types of tumours, such as hepatic and extrahepatic angiosarcomas, hepatocellular tumours, mammary-gland carcinomas, Zymbal-gland tumours, nephroblastomas, brain tumours, pulmonary adenomas and nasal olfactory carcinomas, as well as a series of non-neoplastic lesions in several organs, have been found in a number of animal species after prolonged exposure to atmospheres containing VCM at sufficiently high concentrations (Basalaev, Vazin & Kotchetkov, 1972; Feron & Kroes, 1979; Lee, Bhandari, Winston, House, Dixon & Woods, 1978; Maltoni & Lefemine, 1975; Suzuki, 1978; Torkelson, Oyen & Rowe, 1961; Williamson, 1976; Winell, Holmberg & Kronevi, 1976).

Residual VCM present in extruded polyvinyl chloride (PVC) has been shown to be liable to migrate into PVC-packed foods and drinks (Daniels & Proctor, 1975; Fuchs, Gawell, Albanus & Slorach, 1975; Potter, 1976; Randolph, 1973; Williams & Miles, 1975). There is still only a small amount of data on the oral toxicity of VCM. In a 13-wk toxicity study, in which the monomer was dissolved in soya-bean oil and administered to rats at levels of 0, 30, 100 or 300 mg/kg body weight, once daily on 6 days/wk, the no-effect-level was conservatively placed at 30 mg/kg body weight, but was probably higher since the effects at the higher doses were of doubtful toxicological significance (Feron, Speek, Willems, van Battum & de Groot, 1975). From preliminary observations it appeared that a more practical method for chronic oral exposure of rats to VCM is the feeding of diets containing PVC powder with a high VCM content (Feron *et al.* 1975). Therefore, in the present lifespan study, PVC powder containing VCM was incorporated in the diet at levels to give planned daily intakes of 1, 3 or 10 mg VCM/kg body weight. This method does not allow dietary VCM intakes much higher than 10 mg/kg body weight/day, a dose that is, however, very high in comparison with a recent estimate of the maximum likely oral daily intake by man, i.e. 0·0017 μg VCM/kg body weight day or 0·1 μg VCM/

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FYI

NEUROLOGICAL CHANGES IN VINYL CHLORIDE-EXPOSED WORKERS

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Vinyl chloride (VC) toxicity for the human organism is not still fully clear. The occupational exposure to VC is linked with the development of liver hemangiosarcomas, or with other malignant processes of varying locality. Some authors diagnose changes in terms of scleroderma, universally are described roentgenologically detected lesions of interphalangeal joints and zonal osteolysis. They are described in association with Raynaud's syndrome (12, 10, 1, 4, 5 and others). Lange with his colleagues (12) describes angiologically detectable constriction of digital arteries, stenosis or partial occlusion of phalangeal blood vessels. Described are also various types of dysesthesia in fingers, particularly cold and numbness sensations. Also Byczkowska (3) reports frequent occurrence of finger paresthesia, whitening of fingers, but also of palms and soles, and other symptoms of peripheral vasomotor disorders.

Neurological manifestations are described only sporadically. Spirtas and colleagues (16) emphasize particularly the narcotic action of VC at higher peak exposure concentrations. This manifests itself by vertigo, nausea and headache pains. Mentioned are also hand paresthesiae (princkling, formication). Langauer-Lewowicka (11) analyzes also the clinical symptoms in her group of 200 examinees who showed most frequently signs of cerebellar symptomatology. She recorded frequent occurrence of headaches and sleep disorders, but also trigeminal neuralgia.

Because of a lack of more detailed neurological studies among the VC-exposed persons, we conducted field investigations among the occupationally exposed workers in a plant where there was six years before put into operation a workshop with a considerable VC hazard.

MATERIAL AND METHODS

The group of examinees consisted of 293 workers (263 males and 30 females), age 18—58 years, mean age 32.8 years. Of these 76 % were below 40. The average time of exposure was 2.8 years (range from 2 months to 6 years). After consultations with plant physician and plant toxicologist the group was divided into two subgroups according to the level of exposure. The subgroup of high-risk workers, in which the tentatively established maximum allowable concentration of 10 mg . m^{-3} had been frequently and sometimes highly exceeded, involved polymerization workers and some maintenance workers (a total of 109 persons). The subgroup of lower-risk category of workers included those engaged in drying and bagging operations, but even here they were sometimes exposed to high peak exposure concentrations during cleaning and sampling operations, and those from the other plant workshops — combustion, compressors, cracking, chlorination, regeneration — where the exposure risk was relatively low (a total of 184 persons).

All the workers were examined neurologically, some of them repeatedly. A more detailed analysis of subjective complaints was performed on the basis of EOD and NS questionnaire surveys. Electroencephalographic examination with photostimulation was made in 232 persons (255 recordings). The group of controls consisted of 46 persons without exposure to toxic substances.

RESULTS

An overview of subjective complaints is presented in Table 1. Headaches occur frequently, but they are less frequent than in the control group. The incidence of gastrointestinal disorders and other neurovegetative disorders (palpitations, retrosternal pressure sensations) are significantly higher than in controls. Psychic disturbances were observed only in those exposed.

Table 1. Overview of subjective complaints in workers occupationally exposed to vinyl chloride, in a comparison with controls

Complaints	VC — exposed		Controls	
	number	%	number	%
Headache	46	15.7	9	19.6
Sleep disorders	16	5.5	2	4.4
GIT disorders	20	6.9	1	2.2
Vertigo	3	1.0	1	2.2
Psychic disturbation	13	4.5	0	0.0
Dysesthesia	9	3.1	1	2.2
Palpitations	14	4.8	0	0.0
Total number of examinees	293	100.0	46	100.0

Significant differences were observed between the two subgroups of exposed workers divided according to the level of exposure (Table 2). The subgroup of more exposed workers showed a higher incidence of headaches and

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Table 2. Overview of subjective complaints in workers occupationally exposed to vinyl chloride, relation to the level of exposure

Complaints	Total		More exposed		Less exposed	
	number	%	number	%	number	%
Headache	46	15.7	19	17.4	27	14.7
Sleep disorders	16	5.5	7	6.4	9	4.9
GIT disorders	20	6.9	11	10.1	9	4.9
Vertigo	3	1.0	2	1.8	1	0.5
Psychic disturbation	13	4.5	6	5.5	7	3.8
Dysesthesia	9	3.1	7	6.4	2	1.1
Palpitations	14	4.8	5	4.6	9	4.9
Total number of examinees	293	100.0	109	100.0	184	100.0

gastrointestinal disorders, and furthermore, of dysesthesia of extremities. There was observed also a certain correlation with the length of exposure (Table 3). In persons with the exposure time longer than 4 years, the incidence of headaches was double the incidence in the group with a shorter time of exposed for more than 4 years. Sleep disorders, gastrointestinal complaints, vertigo and psychic disturbances were also more frequent in those with a longer time of ex-

Table 3. Overview of subjective complaints in workers occupationally exposed to vinyl chloride, relation to the length of exposure

Complaints	Total		Exposure longer than 4 years		Exposure shorter than 4 years	
	number	%	number	%	number	%
Headache	46	15.7	24	23.8	22	11.0
Sleep disorders	16	5.5	8	7.9	8	4.2
GIT disorders	20	6.9	9	8.9	11	5.7
Vertigo	3	1.0	3	3.0	0	0.0
Psychic disturbation	13	4.5	8	7.9	5	2.6
Dysesthesia	9	3.1	8	7.9	1	0.5
Palpitations	14	4.8	4	4.0	10	5.2
Total number of examinees	293	100.0	101	100.0	192	100.0

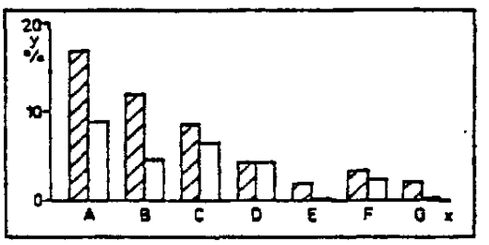
posed workers is characterized in Table 4. The group of more exposed workers showed a significantly lower per cent of normal findings and a higher per cent of more severe findings than the group of less exposed workers.

Graph 1 presents incidence of the most frequent, objectively diagnosed syndromes detected in exposed and control groups. The most frequent was the lesion of peripheral neurons, either motor or sensory, or both of them [16.8 % : : 8.7 %]. Diagnosed were impairments of muscle tonus or trophicity, reduction or loss of tendon and bone reflexes, abnormal sensitivity. Compared to controls,

Table 4. Severity of objectively diagnosed changes in workers occupationally exposed to vinyl chloride in relation to the level of exposure

Severity of changes	Total		More exposed		Less exposed	
	number	%	number	%	number	%
Normal	165	57.0	50	46.0	115	62.5
Light changes	112	38.0	49	45.0	63	34.2
Manifest changes	16	5.0	10	9.0	6	3.3
Total number of examinees	293	100.0	109	100.0	184	100.0

the group of exposed workers showed also more frequently the symptomatology of peripheral neurovegetative disorders (12 % : 4.4 %), specifically acrohypothermy, acrohyperhidrosis or whitening of fingers, associated with dysesthesia.



Graph 1: Objectively diagnosed changes in VC-exposed workers in a comparison to controls. X-axis — objectively diagnosed changes: A — peripheral neuron lesions, B — peripheral neurovegetative symptomatology, C — cerebellar symptomatology, D — vestibular symptomatology, F — extrapyramidal symptomatology, G — disperse central symptomatology. Blank column — group of controls, hatched column — group of VC-exposed. Y-axis — % of examinees

Graph 2 shows objectively diagnosed symptoms in relation to the level of exposure. A marked difference is in the incidence of peripheral neuron lesions: more exposed workers are affected more than twice as often (25.6 % : 11.8 %). Celebellar and vestibular syndrome is also more frequent (10 % : 7.6 % and 6.4 % : 3.3 %, respectively). There are also certain indications of a correlation with the length of exposure, see Graph 3: those with more than 4 years of exposure have more frequently peripheral neuron lesions (22.8 % : 13.8 %) and cerebellar impairments (13.9 % : 5.7 %). Frequency of the vestibulocerebellar syndrome is also higher (5 % : 0.5 %) in these persons.

The results of EEG examinations of exposed and 81 non-exposed control workers are compared in Table 5. The per cent of abnormal EEG recordings in the group of exposed workers is higher than in the control group; the EEG abnormities detected in the controls were always least severe. Abnormities

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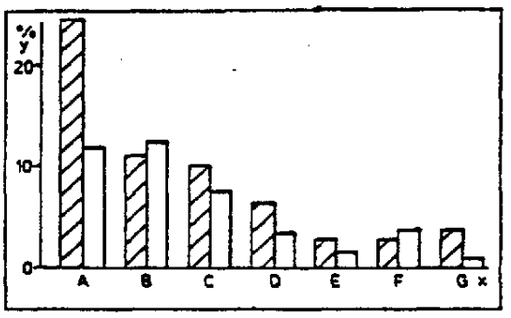
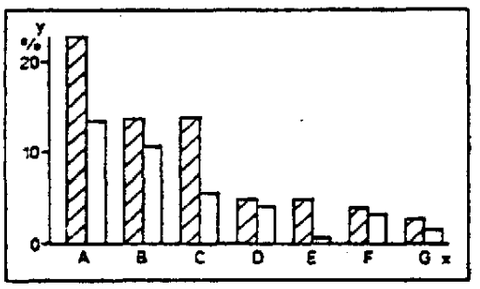
diagnosed in VC-exposed workers were predominantly episodic, in 5 cases combined with the diffuse abnormity. Three EEG recordings revealed only diffuse abnormities. Relatively frequent was also the presence of sleep waves (in 46.5 % of cases). In 16 % of workers the sleep activity manifestations were of



Graph 2: Objectively diagnosed changes in VC-exposed workers in relation to the level of exposure. X-axis objectively diagnosed changes: A-D see Graph 1. Blank column — lower exposure levels, hatched column — higher exposure levels. Y-axis — % of the total number of exposed subjects.

a higher degree of severity (2c to 3, according to Roth (13)). Significant differences were observed also in the photostimulation reaction that was normal only in 40 % of cases. The most frequent was extension of photic driving towards beta and theta waves (in 43.4 % of cases).

The additionally conducted N5 and EOD (6, 7, 8, 9) questionnaire surveys were used to improve analysis of subjective complaints and to complement



Graph 3: Objectively diagnosed changes in VC-exposed workers in relation to the length of exposure. X-axis — objectively diagnosed changes: A-D see Graph 1. Blank column — exposure shorter than 4 years, hatched column — exposure longer than 4 years. Y-axis — % of the total number of exposed subjects.

anamnestic data. The questionnaire N5 examines superficial personal traits as well as certain clinical symptomatology, particularly neurovegetative syndrome, neurasthenic, depressive and anxiety-phobic symptoms, and the so-called toxic syndrome. Data provided by this type of questionnaire were suggestive of

Table 5. Severity of EEG changes in workers occupationally exposed to vinyl chloride, in a comparison to controls

EEG changes		Exposed		Controls	
		number	%	number	%
Normal		148	63.8	57	70.4
Suspect		48	20.7	19	23.4
Abnormal	slight	30	12.9	5	6.2
	medium	6	2.6	0	0.0
	total	36	15.5	5	6.2
Total		232	100.0	81	100.0

a higher frequency of sleep disorders (38 %) than originally revealed by anamnestic data, highly frequent (5 % level of significance) was also somnolence (76 %), which had not been also indicated in personal histories. More frequent were also feelings of bad performance, fear of loosing life or health. Furthermore, the frequency of hyperhidrosis was also very high (73 %). The Eyseneck personality questionnaire examines neuroticism. It reveals subjective tendencies that are evaluated by the examinee and confronted with the objective reality. In the examined group there were not detected any significant deviations from the norm; increased neuroticism could not be demonstrated.

DISCUSSION

Clinical examination of VC-exposed workers revealed significant changes predominantly in neurologic symptomatology. Some of the subjective complaints, such as headaches, vertigo, sleep disorders or increased sleepiness during the day, as revealed by questionnaire N5, are suggestive of the narcotic action of VC, similarly as the occurrence of the cerebellar and/or vestibulocerebellar symptomatology. These changes have been already described by Spirtas and colleagues (16), Langauer-Lewowicka (11), but also by Schwartzová (15) and others. This characteristic symptomatology was also described in our previous studies concerned with the occupational exposure to trichloroethylene, benzene and other organic solvents (17, 18, 20). Here we also observed a high incidence of dysesthesia after exposures to some solvents, particularly to benzene. We ascribed it either to peripheral vasomotor changes, or — at least in some cases — to initial phases of polyneuropathy. In case of VC the presence of peripheral vasomotor changes is evidently very significant: according to literature data

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and to our own experience these changes are frequently associated with Raynaud's syndrome and may presumably lead to even more severe consequencies in terms of stenosis or occlusion, as described by Lange (12). Peripheral nerve lesions diagnosed in our group of VC-exposed examinees could be then explained by a direct neurotoxic action of VC, or as a consequence of hypoxia accompanying more severe vasomotor changes in the periphery.

The narcotic action of VC can be either transitory, inducing only reversible changes in the brain function, or persistent, causing more permanent, sometime irreversible changes in the CNS. Slight functional changes manifest themselves in EEG recordings by waves typical for various stages of sleep, as confirmed in a relatively high per cent (46.5 %) of cases in our group of examinees as well as in some of the examined subjects exposed to other organic solvents (19, 21, 22). Detection of episodic or diffuse EEG abnormalities is rather more serious and may be indicative of chronic changes in mediobasal and/or cortical brain structures. In our group of examinees, the joint episodic and diffuse abnormality occurred in 15.6 % of workers. This frequency is in agreement with the cited literature data as well as with our previous experience. This leads us to a conclusion that even VC, particularly at higher exposure concentrations, can produce neurotic changes in the above described brain structures.

VC-induced pathophysiological changes are believed by some authors to manifest themselves by the central neurovegetative dysregulation, as a result of changed hypothalamus functions (2). This localization, presumed by these authors on the basis of their experimental studies, seems to be in agreement with our findings of EEG episodic abnormalities.

We also believe that even FS reaction changes, recorded in our group of exposed workers, may be of importance in the early diagnosis of VC-induced damage. Comparable FS reaction changes were also described by Rouskovâ (14) in persons exposed to other toxic agents.

CONCLUSIONS

1) Exposure to VC may lead, besides to other changes described in the literature, also to lesions of the nervous system. The onset and development of these neurologic changes depend on the VC exposure level and on the length of exposure.

2) Some of the neurologic manifestations are caused by the narcotic action of VC, such as certain subjective complaints and cerebellar and/or vestibulocerebellar syndrome. These symptoms can be transitory or persistent.

3) Among the important manifestations that are characteristic for VC action is, no doubt, the peripheral vasomotor symptomatology, sometimes in combination with the Raynaud's syndrome described in the literature. These vasomotor changes in the periphery may further develop, leading consequently to

more severe lesions of peripheral blood vessels. Equally important are the general neurovegetative manifestations (gastrointestinal and cardiovascular disorders, hyperhidrosis, etc.) that might result from the central neurovegetative dysregulation. Important are also symptoms of peripheral neuron lesions caused by a direct neurotoxic action of VC or by hypoxia-related mechanisms.

4) Episodic abnormality in EEG recordings seems to agree with the assumed involvement of hypothalamic structures (Basalajev and colleagues). It occurs even at exposure to the other types of organic solvents (15, 19, 21, 22) and may be indicative of a more diffuse affliction of mediobasal and cortical structures of the brain. Less severe manifestations of EEG sleep activity can be ascribed to the nacrotic action of VC, more pronounced sleep manifestations accompanied with abnormal EEG changes may be suggestive of more persistent changes in the CNS.

5) Neurological changes have not been so far sufficiently accentuated in the professional literature and, therefore, the monitoring of workers at risk is not conducted systematically and by suitable methods. It is necessary to ensure a neurological prevention in these occupationally exposed workers. Of the supplementary methods of examination there are recommendable, both for prevention and research purposes, to use EEG examination with photostimulation, questionnaires N5 and EOD, and electromyographic examination.

SUMMARY

Neurological examinations were conducted in 293 workers occupationally exposed to vinyl chloride. Subjective complaints were evaluated on the background of N5 and EOD questionnare survey analysis, EEG examinations, including photostimulation, were performed in 232 persons. The control group comprised 46 nonexposed subjects. Average time of exposure was 2.8 years, the longest time of exposure was 8 years.

Among the most frequent subjective complaints were headache, neurovegetative disorders and dysesthesiae, among objective findings dominated cerebellar and/or vestibulocerebellar syndrome, lesions of peripheral neurons and peripheral neurovegetative symptomatology. Subjective and objective symptoms were found to depend on the exposure level and the time of exposure.

EEG examinations confirmed in 15.5 % of cases abnormities, predominantly episodic, sometimes combined with the diffuse abnormality. 46.5 % of the exposed showed presence of sleep activity as a consequence of VC narcotic action. The episodic EEG activity could be ascribed to lesions of mediobasal structures, or even to changes in brain cortex.

Our data have confirmed that vinyl cloride has a considerable impact on the human nervous system. Most frequent are lesions of vestibulocerebellar system and vigility disorders due to VC narcotic action. Frequent occurrence of peripheral symptomatology can be explained by a direct neurotoxic action of VC, or as a consequence of hypoxia caused by peripheral vasomotor changes.

As a rule, regular check-ups of VC-exposed workers do not include systematic neurological examinations. The systematic neurologic prevention, based on the assessment of clinical, EEG and/or EMG examinations, should become obligatory. Supplementary use of N5 and EOD questionnaire surveys is highly advisable.

RÉSUMÉ

Stýblová, V., Lambl, V., Chumchal, O., Kellerová, V., Paško-vá, V., Vítovcová, J., Zlab, L.: L'image neurologique chez les sujets exposés au chlorure de vinyle

Il a été étudié d'une manière complexe l'image neurologique chez 293 sujets exposés au chlorure de vinyle. Des troubles subjectifs ont été analysés au plan détaillé à l'aide des anquêtes EOD et N5. Il a été mis en évidence un effet neurotoxique significatif produit par chlorure de vinyle qui dépend de la qualité et de la quantité de l'exposition subie.

Les troubles subjectifs rencontrés le plus souvant: maux de tête, symptômes végétatifs et dysesthésie. Les données objectives témoignent pour une affection du système vestibulocérébelleux et pour celle du neurone périphérique et de l'innervation périphérique végétative. La symptômatologie périphérique peut résulter de l'effet toxique direct produit par chlorure de vinyle aussi bien que du mécanisme d'hypoxie ayant lieu lors des changements vasomoteurs périphériques.

Des donnés issues de l'EEG témoignant une activité de sommeil chez 46,5 % de sujets démontrent un effet narcotique du chlorure de vinyle. L'activité épisodique (chez 15,5 %) associée parfois à l'anomalie de diffusion pourrait s'expliquer par une atteinte des structures médiobasales, même liée aux changements du cortex.

Les sujets exposés à l'influence du chlorure de vinyle ne se soumettent, jusqu'à ce jour, aux examens systématiques au plan neurologique. Il est nécessaire de poursuivre, dans ce cas, une prophylaxie neurologique étudiant l'image clinique, les données issues de l'EEG ou même de l'EMG. Il est utile d'employer les anquêtes EOD et N5.

ZUSAMMENFASSUNG

Stýblová, V., Lambl, V., Chumchal, O., Kellerová, V., Paško-vá, V., Vítovcová, V., Zlab, L.: Neurologisches Bild bei den dem Vinylchlorid exponierten Arbeitenden

Man beobachtete komplexerweise das neurologische Bild bei 293 Arbeitenden, die Vinylchlorid exponiert waren. Subjektive Schwierigkeiten analysierte man eingehender mit Hilfe der EOD- und N 5-Fragebogen. Dabei hat man eine signifikante neurotoxische Einwirkung von Vinylchlorid nachgewiesen, die von der Intensität und Dauer der Exposition abhängig ist.

Die häufigsten subjektiven Schwierigkeiten waren Kopfschmerzen vegetative Symptome und Dysesthäsie. Der objektive Befund zeugt von der Affektion des Vestibularzerebellarsystems, ferner von der Affektion des peripheren Neurons und der peripheren vegetativen Innervation. Die periphere Symptomatologie kann man erklären sowohl als direkte Einwirkung von Vinylchlorid, als auch den hypoxischen Mechanismus bei peripheren vasomotorischen Veränderungen.

In dem EEG-Befund stellte man bei 46,5 % Tiele der Gesamtheit die Schlafaktivität fest, die die narkotische Einwirkung von Vinylchlorid dokumentiert. Die episodische Aktivität (bei 15,5 %) manchmal in Verbindung mit Diffusionsabnormität könnte man durch Affektion von mediobasalen Strukturen, gegebenenfals durch Kortexveränderungen erklären.

Die Vinylchlorid exponierten Arbeitenden werden bisher systematisch vom neurologischen Standpunkt nicht beobachtet. Die Verfasser halten die gezielte neurologische

Vorbeugung in Verbindung mit Beobachtung des klinischen Bildes, des EEG- eventuell auch des EMG-Befundes für notwendig. Sehr geeignet ist die Anwendung der EOD- und N 5-Fragebogen.

RESUMEN

Stýblová, V., Lambl, V., Chumchal, O., Kellerová, V., Paško-vá, V., Vítovcová, V., Zlab, L.: El cuadro neurológico en trabajadores expuestos al vinilcloruro

Se ha examinado globalmente el cuadro neurológico en 293 trabajadores expuestos al vinilcloruro. Las dificultades subjetivos se las analizó detalladamente mediante los cuestionarios EOD y N 5. Se mostró el resultado neurotóxico marcado del vinilcloruro, el que dependía de la altura y duración de la exposición. Las dificultades subjetivas más frecuentes eran los dolores de la cabeza, los síntomas vegetativos así que la disestesia. El hallazgo objetivo muestra la afectación del sistema vestibulocerebelar, así que la de la neurona vegetativa periférica y de a inervación vegetativa periférica. La sintomatología periférica la puede explicar tanto por el efecto tóxico directo del vinilcloruro, como por el mecanismo hipóxico con los cambios vasomotóricos periféricos.

Se halló en hallazgos electroencefalográficos una actividad del sueño en el 46,5 p. c. del conjunto, lo que prueba el resultado narcótico del vinilcloruro. La actividad epizódica (en el 15,5 p. c.), a veces en la combinación con la anormidad difusa podría se explicar por afectación de las estructures mediobasales, eventualmente por cambios de la epidermis.

Los trabajadores expuestos al vinilcloruro no son aún examinados neurológicamente de manera sistemática. Hace falta que se haya realizado neurológica prevención encaminada incluso el cuadro clínico, el hallazgo electroencefalográfico, eventualmente el electromiográfico. Se recomienda usar los cuestionarios EID y N 5.

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Vinyl chloride

4449
Aust. N.Z. J. Med., 11, No. 3, 1981, p. 290–2
ISOPHORONE DIISOCYANATE INDUCED RESPIRATORY DISEASE (IPDI)
C.W. Clarke; P.M. Aldons
A 50-yr old male spray painter developed severe asthma following exposure to paint containing IPDI.

4450
Brit. J. Dermatol., 105, (Suppl. 21), 1981, p. 19–21
VINYL CHLORIDE DISORDER
A.E. Walker
A review on diseases caused by occupational exposure to vinyl chloride air pollution. 9 refs.

4451
Mutat. Res., 83, No. 1, 1981, p. 137–44
CHROMOSOMAL ANALYSIS IN VINYL CHLORIDE EXPOSED WORKERS: COMPARISON OF THE STANDARD TECHNIQUE WITH THE SISTER-CHROMATID EXCHANGE TECHNIQUE
D. Anderson; C.R. Richardson, et al.
A group of workers occupationally exposed to vinyl chloride and controls were examined for the presence of chromosomal aberrations or sisterchromatid exchanges in their peripheral lymphocytes. These people comprised a 2nd sampling from a group of exposed workers and controls first examined 18 months earlier. The vinyl chloride exposed workers showed levels of chromosomal aberrations elevated above those of the controls, but there was only a slight increase in sister-chromatid exchanges. Sister-chromatid exchanges (SCEs) were also examined from in vitro cultures of lymphocytes exposed to vinyl chloride, both with and without metabolic activation. There was no increase in SCEs in vitro without metabolic activation, but there was a marked increase with metabolic activation and this increase was shown to be independent of cell-cycle phase. The small increases of SCEs in workers were not due to the inability of vinyl chloride to induce SCEs in human lymphocytes but were probably because of low exposures and SCE levels could have returned to normal relatively quickly after exposure.

4452
Arch. Dermatol., 117, No. 8, Aug. 1981, p. 452–3
OCCUPATIONAL HISTORY AND ANGIOSARCOMA (LETTER)
D.F. Rubin
Occupational disease; viny chloride/adverse effects.

4453
Mutat. Res., 83, No. 2, 1981, p. 271–89
IN VIVO AND IN VITRO ETHYLENE OXIDE EXPOSURE OF HUMAN LYMPHOCYTES ASSESSED BY CHEMICAL STIMULATION OF UNSHEDULED DNA SYNTHESIS
R.W. Pero; B. Widegren, et al.

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4454
Teratology, 23, No. 3, 1981, p. 317–323
TERATOGENIC EFFECTS OF ALIPHATIC NITRILES
C.C. Willhite; V.H. Ferm; R.P. Smith
Acrylonitrile; Animal; Proprionitrile.

4455
Teratology, 23, No. 3, 1981, p. 325–33
MORPHOGENESIS OF AXIAL SKELETAL (DYSTRAPHIC) DISORDERS INDUCED BY ALIPHATIC NITRILES
C.C. Willhite; M. Morin-Padilla; V.H. Ferm; R.P. Smith
Acrylonitrile; Animal; Proprionitrile.

From K.H. Ferber, Wm. J. Hill & D. A. Cobb. AIHA Jnr. Jan 1976 pgs 61–68
Allied Chemical.
Benzidene.

TABLE I
Summary of the Bladder Tumor Incidence Numerators for the Exposed Population at a Dye Plant

NUMERATOR	BENZIDINE EXPOSURE ONLY	EXPOSURE TO BENZIDINE AND/OR OTHER POTENTIAL CARCINOGENIC AGENTS*
No. of reported cases of bladder tumor (1930-May, 1975)	36	115
No. of cases occurring in group first exposed prior to 1955 and diagnosed by May, 1975	36	115
No. of cases occurring in group first exposed between 1935-54 and diagnosed by 1955 (See Figures 1 & 2)	10	19
No. of cases occurring in group first exposed since 1955	0	0

*Including beta naphthylamine, crude alpha naphthylamine and ortho toluidine.

been effective in preventing bladder tumors. Because of the long average induction period of about 18 years,[3] earlier comparisons would have been statistically unconvincing.

Statistical analysis of case data

A frequent problem in performing a statistical analysis to determine if there has been a significant reduction in morbidity, e.g. bladder tumors, is the paucity of epidemiological data on the exposed population. The "numerators" or data on the bladder tumor cases may be known reasonably well through medical reports and compensation claims (See Table I). However, the "denominators" may not be well

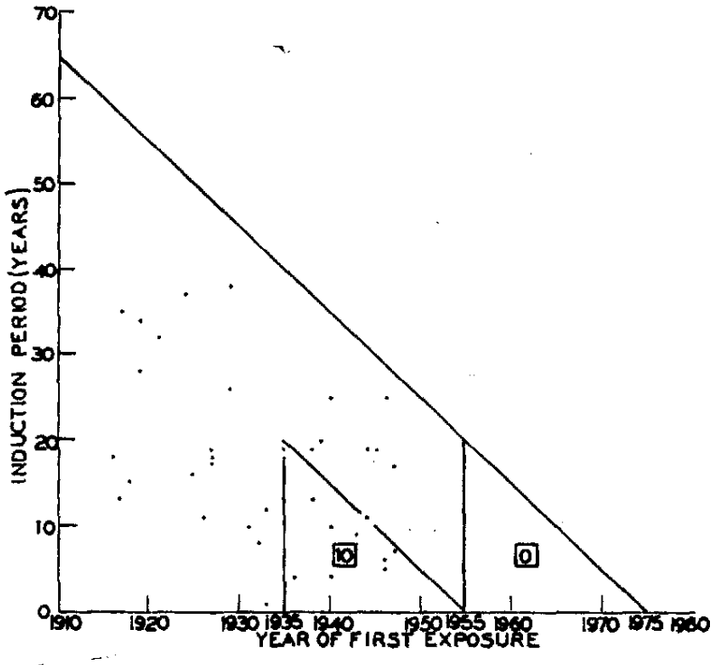

Figure 1—Reported number of bladder cases, benzidine exposure only, 36 cases.

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Memorandum from W.D.H.

Corporate Medical Department
W.D. Harris, Industrial Toxicologist

~~JDF~~ BRL } I came across this in my unfinished file. The chart attached explains the method of plotting. I haven't brought it up to date this past year. It seems hard to believe that we won't have at least one case of angiosarcoma, but the way statistics work we could have 0 – 2 cases. It is pretty unlikely we will have many cases.

~~[illegible]~~

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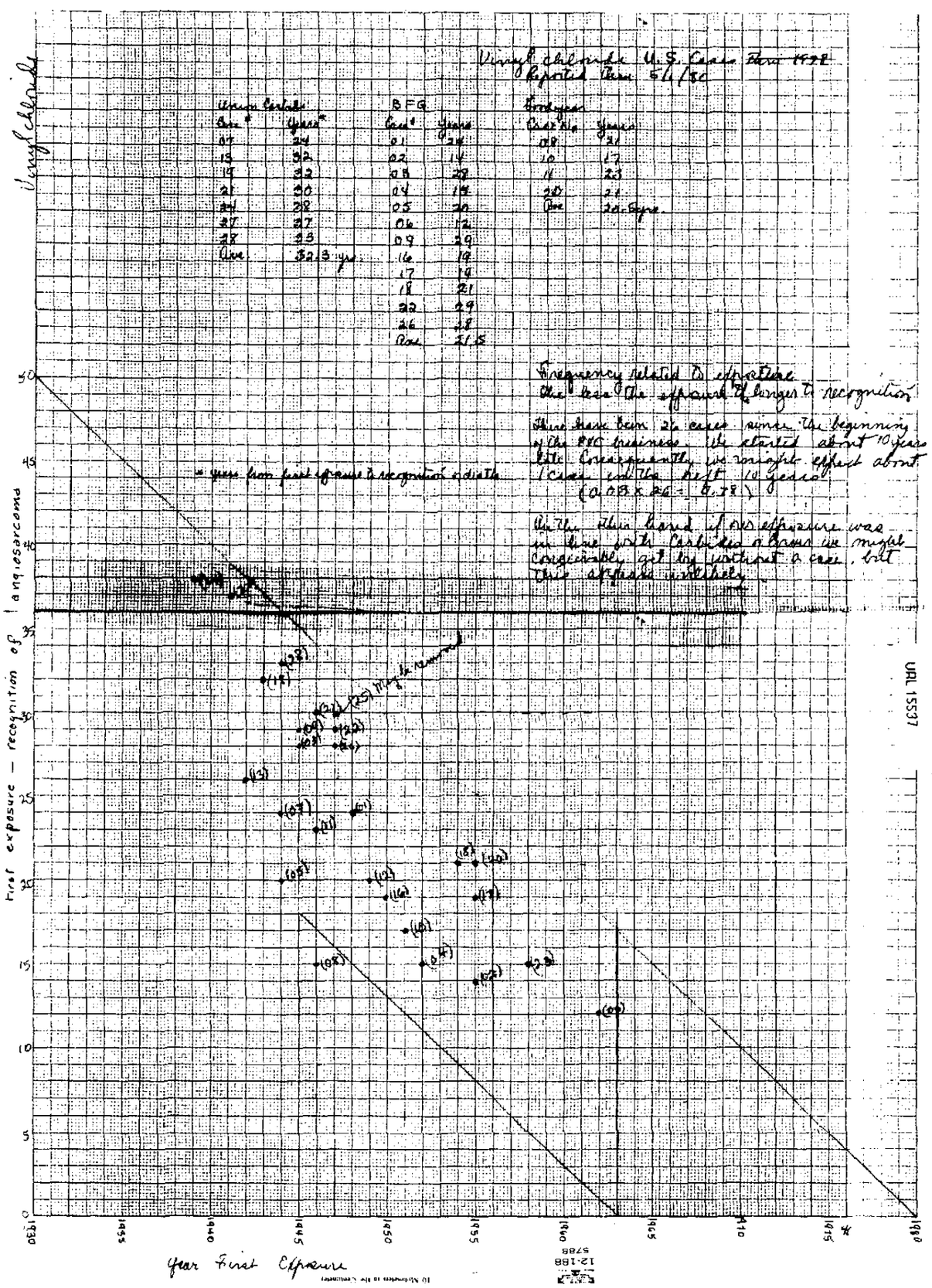

Vinyl Chloride		BFG		Goodyear	
Case #	Years*	Case #	Years	Case No.	Years
07	24	01	24	09	21
13	32	02	14	10	17
19	32	03	28	11	23
21	30	04	18	20	21
24	28	05	30	Ave	20.5 yrs.
27	27	06	12		
28	33	09	29		
Ave	30.3 yrs.	16	19		
		17	14		
		18	21		
		22	29		
		26	28		
		Ave	21.5		

Frequency related to exposure
The less the exposure the longer to recognition

Since there have been 24 cases since the beginning of the PVC business, the latency about 10 years late. Consequently, we might expect about 1 case per the next 10 years.
(0.08 x 26 = 0.78)

On the other hand if the exposure was in line with Carbide & Borden we might conceivably get by without a case, but this appears unlikely.

TOXICOLOGY AND APPLIED PHARMACOLOGY 62, 1-10 (1982)

The Effect of Repeated Vinyl Chloride Exposure on Rat Hepatic Metabolizing Enzymes[1]

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The Effect of Repeated Vinyl Chloride Exposure on Rat Hepatic Metabolizing Enzymes. DU, J. T., TSENG, M. T., AND TAMBURRO, C. H. (1982). *Toxicol. Appl. Pharmacol.* 62, 1-10. Sprague-Dawley rats were exposed to 2.8% vinyl chloride for 2 (70 hr), 4 (140 hr), and 6 (210 hr) weeks to determine the sequential biochemical changes related to the oxidation and detoxification ability of hepatic tissue. Glutathione-*S*-transferase(s) activity using 1,2-epoxy-(*p*-nitrophenoxy)propane and *p*-nitrobenzyl chloride as substrates was elevated 17 to 24, 28, and 35 to 42% after 2, 4, and 6 weeks of exposure, respectively, suggesting enzyme(s) induction. Reduced glutathione, the major substrate required to conjugate the toxic metabolites of vinyl chloride, was also consistently elevated. Similarly, the activity of glutathione reductase, the enzyme necessary for the regeneration of reduced glutathione from its oxidized form, was also increased following vinyl chloride exposure. Cytochromes *P*-450, the major protein involved with vinyl chloride metabolism, was reduced after vinyl chloride exposure, confirming reports of others that vinyl chloride metabolites destroy *P*-450. No abnormalities of standard clinical biochemical blood tests of liver function were found during 6 weeks of vinyl chloride exposure. The only consistent ultrastructural modification was the dilation of endoplasmic reticulum. The biochemical and ultrastructural alterations could reflect early hepatocellular adaptation to vinyl chloride exposure.

Vinyl chloride, at high concentrations, has been shown to be carcinogenic in both laboratory animals (Maltoni and Lefemine, 1975; Viola *et al.*, 1971) and man (Creech and Johnson, 1974). Present data support the metabolism of vinyl chloride by hepatic microsomal mixed-function oxidase system into toxic intermediates, chloroethylene oxide (Bolt *et al.*, 1975; Hefner *et al.*, 1975; Kappus *et al.*, 1976) and chloroacetaldehyde (Gross and Freiberg, 1969). These two intermediates are considered to be the ultimate carcinogens (Barbin *et al.*, 1975; Jaeger *et al.*, 1974b; Van Duuren, 1975), to be mutagenic in bacterial systems (Elmore *et al.*, 1976; Greim *et al.*, 1975; Malaveille *et al.*, 1975; McCann *et al.*, 1975), to act as an alkylating agent by reacting with adenosine (Barbin *et al.*, 1975) and cytidine (Laib and Bolt, 1978), and to bind with protein (Bolt *et al.*, 1976; Kappus *et al.*, 1976; Watanabe *et al.*, 1978). Detoxification of these metabolites occurs mainly by conjugation with glutathione and is catalyzed by hepatic glutathione transferases; the conjugates are excreted in the urine as substituted cysteine derivatives (Watanabe *et al.*, 1976b,c; Green and Hathway, 1975, 1977). Chloroacetaldehyde can be further oxidized to chloro-

[1] This work was supported by a grant from the Manufacturing Chemists Association, Washington, D.C. Portions of this study have been presented (Fed. Proc. 37, 1545, 1978).

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Vinyl chloride

The hotline telephone number is toll-free (800) 424-9346, or in Washington, D.C., (202) 382-3000. The agency noted that this is a new local number for the RCRA/SUPERFUND hotline and should be used in place of all previously published hotline numbers.

The hotline only should be used for information on the superfund and not for reporting hazardous substance spills. These must continue to be reported to the National Response Center at (800) 424-8802.

Radioactive Waste

HIGH-LEVEL WASTE RULES TO BE PROPOSED IN FEBRUARY, ACCORDING TO EPA OFFICIALS

Standards and federal radiation guidance for the management and disposal of high-level radioactive wastes and spent nuclear fuel probably will be proposed in mid-February, according to Environmental Protection Agency officials.

According to internal agency documents, which were used in a briefing session presented by agency staff to EPA Deputy Administrator John Hernandez, Subpart A of the rule proposal, Standards for Management and Storage, would extend the exposure limits being developed by the Nuclear Regulatory Commission to waste management operations.

Transportation of wastes would not be included as a waste management operation, according to the documents.

Subpart B, Standards for Disposal, would set limits on projected releases from stored wastes over a 10,000-year period.

The appendix to the standards would contain the Federal Radiation Guidance for Disposal, according to the briefing materials.

Gordon Burley, director of EPA's Office of Radiation Programs, told BNA Jan. 20 that the standards are under high-level agency review and are expected to be issued in about four weeks. Burley said the proposal also is being reviewed by OMB.

Administration

EPA NAMES 10 NEW ATTORNEYS, ESTABLISHES CRIMINAL ENFORCEMENT UNIT

Ten attorneys were appointed to fill key slots in the Environmental Protection Agency's recently reorganized enforcement section, and a new criminal enforcement unit was created to crack down on flagrant violations of environmental law, according to a Jan. 19 agency announcement.

Enforcement counsel William A. Sullivan, Jr., said the new appointments to the reorganized Office of Enforcement Counsel (Current Report, Dec. 11, 1981, p. 995) include Sanford Harvey Jr., deputy associate enforcement counsel, who will be in charge of pesticides and toxics enforcement and Michael S. Alushin, director of the Office of Special Projects, who will supervise superfund expenditures for hazardous waste sites.

Other enforcement appointments included:

- Geoffrey Grubbs, as director of the Office of Enforcement Policy;
- Gerald Bryan, as director of the Office of Legal Operations; and,
- Peter G. Beeson, as director of the Office of Criminal Enforcement.

Criminal Enforcement Unit

The agency also announced the hiring of 25 experienced criminal investigators to form the core of a new criminal enforcement unit that will crack down on flagrant violations of environmental laws, including illegal discharges of wastes into waterways, so-called midnight dumping of toxic chemicals, and deliberate destruction or falsification of environmental records.

The new Office of Criminal Enforcement will focus on activities that have resulted in substantial environmental harm and human health hazard and on those reflecting willful contempt of court-ordered consent decrees, according to EPA Administrator Anne M. Gorsuch.

Health Hazards

CANCER DEATHS OF FORMER EMPLOYEES LINKED TO SPECIFIC MONSANTO WORK SITES

Cancer deaths among former employees of the Monsanto Chemical Co. plant in Springfield, Mass., may be linked to exposure to materials used at specific work sites, according to a University of Massachusetts study.

The study, conducted by a group of university toxicology graduate students, investigated the deaths of 110 males who worked in the plant and found that 34 had cancer that may have been work related.

Kenneth Rosenman, who headed the study, told BNA Jan. 19 that the research team found increased cancer associated with exposure to vinyl chloride. The death of one former employee was due to liver cancer while several other former workers had mouth, digestive, lymphatic, and lung cancer.

Rosenman said previous studies looked into the cancer deaths of former employees at the Springfield plant, but these studies included all workers, thus "diluting the studies' results." He noted that his study focused only on the worksites where employees were exposed to vinyl chloride and polyvinyl chloride.

Rosenman said that, when he submitted his report to the company last summer, he suggested that it conduct additional occupational studies, concentrating on particular worksites rather than the overall workforce at the Springfield plant.

Pesticides

EPA PUBLISHES TOLERANCE AMENDMENTS, APPROVES CHLORPYRIFOS TEMPORARY TOLERANCE

The Environmental Protection Agency Jan. 15 through 21 established two pesticide tolerances, proposed one tolerance exemption, and granted one temporary tolerance.

Tolerance Amendments

The agency Jan. 20 established a tolerance for bromoxynil at 0.1 parts per million on the following raw agricultural commodities (47 FR 2862): flax seed; flax straw; meat, fat, and meat byproducts of cattle, goats, hogs, horses, and sheep; oat grain; oat forage (green); oat straw; rye grain; rye forage (green); rye straw; wheat grain; wheat forage (green); and wheat straw.

For further information contact Robert Taylor, Registration Division (TS-767C), Office of Pesticide Programs, EPA,

0148-7973/82/$00 50