Carbon disulfide; CASRN 75-15-0

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR Carbon disulfide

File First On-Line 09/30/1987

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	09/30/1987
Inhalation RfC (I.B.)	yes	08/01/1995
Carcinogenicity Assessment (II.)	not evaluated	

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Carbon disulfide
CASRN — 75-15-0
Last Revised — 09/30/1987

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is essential to refer to other sources of

information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

NOTE: The Oral RfD for carbon disulfide may change in the near future pending the outcome of a further review now being conducted by the Oral RfD Work Group.

I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
Fetal toxicity/ malformations **Rabbit Inhalation Teratogenic Study** **Hardin et al., 1981**	NOEL: 20 ppm (62.3 mg/cu.m) converted to 11.0 mg/kg/day LOAEL: None	100	1	1E-1 mg/kg/day

*Conversion Factors: x 6 hour/24 hour x 1.6 cu.m/day breathing rate x 0.5 absorption rate / 1.13 kg bw

I.A.2. Principal and Supporting Studies (Oral RfD)

Hardin, B.D., G.P. Bond, M.R. Sikor, F.D. Andrew, R.P. Beliles and R.W. Niemeir. 1981. Testing of selected work place chemicals for teratogenic potential. Scand. J. Work Environ. Health. 7(Suppl. 4): 66-75.

The data reported in this study were generated at Litton Bionetics, Maryland (under contract to NIOSH). Rats and rabbits were exposed to 20 ppm or 62.3 mg/cu.m (recommended occupational exposure limit) and 40 ppm or 124.6 mg/cu.m of carbon disulfide (CS2) during the entire length of the pregnancy period and also 34 weeks before breeding to simulate occupational exposure.

Hardin et al. (1981) observed no effects on fetal development in rats or rabbits following inhalation exposure to 62.3 or 124.6 mg/cu.m, which corresponds to estimated equivalent oral dosages of 5 and 10 mg/kg for rats, and 11 and 22 mg/kg for rabbits. The highest NOEL from this study, 22 mg/kg for the rabbit, should not be used for an RfD estimate because adverse effects were seen in rabbit fetuses following oral exposure of pregnant does to 25 mg/kg (Jones-

Price et al., 1984a,b). Therefore, the highest NOAEL that is below an effect level is the estimated low dose from the Hardin et al. (1981) inhalation study using rabbits. This dose level, 11 mg/kg, is the most appropriate basis for RfD derivation.

A NCTR-NTP oral study (Jones-Price et al., 1984a,b) observed 25 mg/kg/day in rabbits as an FEL (fetal resorption). Fetotoxicity band fetal malformations in this study were not observed in rats at the lowest level (100 mg/kg/day) of CS2 exposure. The data from this study also suggest that the rabbit fetus is more sensitive than the rat fetus to CS2-induced toxicity. Johnson et al. (1983) reported an epidemiologic study that employed a wide range of exposure with CS2, such as 0.04-5 ppm (mean: 1.2 ppm, low, exposure), 0.04-33.9 ppm (mean: 5.1 ppm, medium exposure) and 0.04-216 ppm (mean: 12.6 ppm, high exposure). In this study the entire population was exposed to a combined exposure of 7.3 ppm over a period of 12 or more years. Of the several clinical findings, the exposed population showed significant alterations in sensory conduction velocity and peroneal motor conduction velocity. However, the data indicated, in the opinion of the authors, that minimal neurotoxicity was evident, since the reduction in nerve conduction velocity was still within a range of clinically normal values and thus not associated with specific health consequences. Additionally, the exposed population had blood lead levels <40 mg/dL and the exposed air alone contained h5S, h5SO4 and tin oxide. Therefore the 7.3 ppm CS2 can be considered as a NOAEL for neurotoxicity. This dose, when extrapolated to an oral dose of 10 mg/kg/day, lends support to the animal NOAEL of 11 mg/kg/day.

I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF — The uncertainty factor of 100 includes 10 for interspecies and 10 for intraspecies variability to the toxicity of this chemical in lieu of specific data.

MF — None

I.A.4. Additional Comments (Oral RfD)

A Bulgarian study (Tabatcova et al., 1983) reported significant fetal malformations in rats exposed to a low CS2 dose of 0.03 mg/cu.m over three generations. Based on these data, an RfD can be drastically lower than the RfDs that could be derived from existing guidelines, epidemiologic data or other experimental data. However, the Bulgarian study did not present information on mode control exposure, animal diet, procedure for selection of F1 and F2 breeding pairs and purity of CS2 (hydrogen sulfide, a teratogenic compound, is often found as a contaminant). In a multigeneration study, toxic effects of a compound can be confounded by the above factors.

I.A.5. Confidence in the Oral RfD

Study — Medium
Database — Medium
RfD — Medium

The principal study was a well-designed multispecies study that provided adequate toxicologic endpoints; a medium confidence is assigned. The data base contains supportive reproductive and epidemiologic studies; therefore, a medium confidence is assigned. The RfD was supported by adequate oral reproductive and epidemiologic studies; however, additional oral chronic toxicity and reproductive studies are needed to support a higher than medium confidence level.

I.A.6. EPA Documentation and Review of the Oral RfD

Source Document — U.S. EPA, 1986

ECAO-Cincinnati-Internal Review, 1986.

Extensive Agency wide review, 1986.

Other EPA Documentation — None

Agency Work Group Review — 06/24/1985, 07/08/1985, 07/22/1985, 08/05/1985

Verification Date — 08/05/1985

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfD for Carbon disulfide conducted in September 2002 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — Carbon disulfide
CASRN — 75-15-0
Last Revised — 08/01/1995

The inhalation Reference Concentration (RfC) is analogous to the oral RfD and is likewise based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory effects). It is expressed in units of mg/cu.m. In general, the RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Inhalation RfCs were derived according to the Interim Methods for Development of Inhalation Reference Doses (EPA/600/8-88/066F August 1989) and subsequently, according to Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA/600/8-90/066F October 1994). RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

NOTE: ****SEE BENCHMARK CONCENTRATION IN DISCUSSION. Discussion of the benchmark dose can be found in the Discussion of Principal and Supporting Studies Section.

I.B.1. Inhalation RfC Summary

Critical Effect	Exposures*	UF	MF	RfC
Peripheral nervous system dysfunction **Occupational Study** **Johnson et al., 1983**	Benchmark Concentration: See Conversion Factors and Assumptions and Principal and Supporting Studies	30	1	7E-1 mg/cu.m

*Conversion Factors and Assumptions: MW = 76.14. Assuming 25 C and 760 mmHg, BMC (mg/cu.m) = 17.7 x 76.15/24.45 = 55.1 mg/cu.m. This is an extrarespiratory effect of a gas exposure. The BMC is based on an 8-hour TWA occupational exposure. MVho = 10 cu.m/day,

MVh = 20 cu.m/day. BMC(HEC) = 55.1 mg/cu.m x (MVho/MVh x 5 days/7 days = 19.7 mg/cu.m.

I.B.2. Principal and Supporting Studies (Inhalation RfC)

Johnson, B.L., J. Boyd, J.R. Burg, S.T. Lee, C. Xintaras and B.E. Albright. 1983. Effects on the peripheral nervous system of workers' exposure to carbon disulfide. Neurotoxicology. 4(1): 53-66.

A cohort of male viscose rayon workers exposed to carbon disulfide (n = 145) was compared with a group of nonexposed artificial fiber plant workers (n = 233) located on the same premises (also reported in NIOSH, 1984). The mean exposure period was 12.1 +/- 6.9 years [mean +/- standard deviation (SD)]. Historical exposure estimates were based on area samples taken since 1957 (5478 samples) and personal samples taken since 1974 (Fajen et al, 1981; NIOSH, 1984). Current exposures were estimated on 250 8-hour personal samples taken for 25 job titles (1-44 samples per job title) during 12 days in early 1979 (Fajen et al., 1981). Based on historical area monitoring and industrial hygiene experience, job titles were divided into low-, medium-, and high- exposure categories prior to the field component of the study. Based on current personal monitoring, the mean carbon disulfide concentrations were estimated to be 7.3 ppm for the combined exposure group and 1.2, 5.1, and 12.6 ppm for the low-, medium-, and high-exposure categories, respectively. These estimates are based on 35, 121, and 94 samples for the low, medium, and high groups, respectively. The median carbon disulfide level for the comparison group was 0.2 ppm. The overall average for the historical area samples was 18 ppm, suggesting that the current personal samples may not be representative of exposure levels in earlier years. This difference also could result from placement of area samplers in areas of expected high exposures. Individuals were assigned to exposure categories based on current job title (n = 40, 61, and 44 in the low, medium, and high groups, respectively). Cumulative exposure index also was calculated as ppm-months, based on historical records of time spent by individual subjects in various job titles and concurrent area monitoring. Cumulative exposures by exposure category were 802, 1002, and 2077 ppm-months for the low, medium, and high groups, respectively (overall cumulative exposure was 1248 ppm-months). The similarity between the low and high categories results because the current measurements for two job titles identified in the low exposure category were higher than any of the measured levels for the medium exposure category (NIOSH, 1984). Workers were excluded on the basis of excess alcohol consumption, diabetes, or elevated blood lead levels. Surface electrodes were used to measure maximum motor conduction velocity (MCV) in the ulnar and peroneal nerves and sensory nerve conduction velocity (SCV) in the sural nerve. Latency and amplitude ratios were calculated. Data were presented after they were normalized for temperature and terminal distance. The numbers of measurements actually recorded varied due to time constraints on the field investigations and were 85, 130, and 137 in the combined exposed cohort and 105, 198, and 199 in the comparison

cohort for the ulnar, sural, and peroneal nerves, respectively. In addition, participants' responses to a medical questionnaire with questions relevant to both central and peripheral nervous system symptoms were tabulated. Neurophysiological test results from the comparison group were compared with the overall exposure group, as well as to the low-, medium-, and high-exposure groups.

Peroneal MCV and amplitude ratio were significantly decreased in the overall exposed group, and the decrease was statistically significant in the high-concentration exposure group vs. the comparison group. A concentration- response trend is evident across exposure categories. When MCV was stratified according to the cumulative exposure index (ppm-months), a significant association was made between this index and decreased MCV. Sural nerve SCV was decreased in the combined exposed groups vs. the comparison groups, however there was no concentration-response relationship in the three exposure groups. No differences in the number of self-reported symptoms related to the peripheral nervous system were found. The decrease in MCV constitutes a LOAEL. When evaluated using the three exposure categories, the only significant effect is shown in the high exposure category. Splitting the exposed group into three exposure levels raises the concern that the resulting smaller numbers of subjects would reduce the power to observe an effect. A power analysis was conducted, and the results indicate that the power was 84% in the mid-exposure group, which is considered to be adequate power to observe an effect. Using the arithmetic mean exposures, this study identifies a LOAEL of 12.6 ppm (39.2 mg/cu.m) and a NOAEL of 5.1 ppm (15.9 mg/cu.m). The duration-adjusted LOAEL and NOAEL are 14.0 and 5.7 mg/cu.m, respectively.

DERIVATION OF A BENCHMARK CONCENTRATION (BMC): A benchmark conentration analysis was performed on the neurophysiological endpoints from Johnson et al. (1983), which are reported as the means and SDs from the three exposure categories described previously. The models used for neurophysiological endpoints were the polynomial model and the Weibull model (ICF Kaiser, Inc., 1990a,b). The models were run both with and without a threshold (i.e., a background intercept) parameter, and an extra risk approach was used. In the current state of development of the BMC approach, there is considerable discussion as to the appropriate level of the benchmark response (BMR) that is used to obtain the BMC, which is the lower bound on concentration at the BMR. A 10% relative change was selected as an appropriate BMR for the nerve conduction velocity measurements because this level is about equal to a difference of one SD from the control, and because a change of about 10% would likely raise concern in a clinical setting. Also, peer reviewer comments suggested that the level of response reported in the Johnson et al. study was of minimal severity and not necessarily adverse (Graham, 1995). Identical values for the BMC were obtained for the polynomial model and the Weibull model (BMC = 11.8 ppm, 37 mg/cu.m), indicating that the BMC for this endpoint is relatively model-independent. The most appropriate BMC based on the group data from Johnson et al. (1983) is from the peroneal MCV [BMC(HEC) = 13.1 mg/cu.m], it is the best data set for BMC analysis

because it has three non- zero responses, and because the model fit is excellent.

The individual data from the Johnson et al. study was obtained by the Chemical Manufacturers Association's Carbon Disulfide Panel, and a BMC analysis was performed and provided to EPA (Price and Berner, 1995). An advantage of using the individual subject data is that the effect of age on nerve conduction velocity can be evaluated. Age was reported by Johnson et al. to be a significant covariate for nerve conduction velocity. For the analysis with individual data, the BMR was defined as a 10% decrease in nerve conduction velocity (for the same reasons cited previously). The resulting BMC was 20 ppm [62.3 mg/cu.m; BMC(HEC) = 22 mg/cu.m], and it is considered superior to the group level analysis because it accounts for the age effect, and because it generally is preferable to use individual data when available.

Further analysis was performed using the individual data from NIOSH that confirms and extends the results of Price and Berner (1995) and evaluates the interaction of age and exposure in explaining the decline in nerve conduction (Setzer, 1995). The data sets used by Setzer were slightly different than those used by Price and Berner because there were some missing and implausible values in the former, which either were replaced by values from the original NIOSH data or were excluded if the discrepancy could not be corrected. Setzer found that the decline in conduction velocity with age was greater in the exposed group than in the control group, suggesting a possible interaction between age and exposure. When this was accounted for, the effect of exposure on conduction velocity was no longer significant. This finding suggests that the individual exposure estimates, based on the current job and on personal monitoring at the time of the study, may not be adequate measures of exposure. When the cumulative exposure estimates were regressed against nerve conduction velocity, a significant effect of exposure was observed.

There are two ways to approach the BMC analysis using cumulative exposure as the independent variable. In the first approach, the individual cumulative exposure is based on the job history of each subject, and the exposure estimates for each job weighted by the time spent at each job. The cumulative exposure in ppm-months for each subject was regressed against nerve conduction velocity, and a BMC in terms of ppm-months was calculated. The BMC was divided by the average exposure duration for the entire exposed population to get a BMC in ppm. Using this approach, the BMC of 2622 ppm-months is obtained, which converts to an average of 17.9 ppm, based on the study average exposure of 12.2 years. The adjusted BMC is 19.9 mg/cu.m. The second approach is to use the average exposure in ppm for each subject, obtained by dividing the individual cumulative exposures in ppm-months by the exposure duration for each individual, as the regression variable, and calculating the BMC in ppm. The BMC was determined to be 17.7 ppm, which leads to an adjusted BMC of 19.7 mg/cu.m. Although the numbers arrived at are essentially the same, it is preferable to use the individual average exposure because all of the individual exposure information is combined prior to modeling, rather than adjusting based on a

group or study average. A similar analysis showed no exposure effect for the ulnar nerve. For the sural nerve, there was a large difference in the effect of age between exposed and control groups that could not be explained by exposure or by any other variable in the data set, so a regression coefficient could not be calculated with confidence. Over the small range of the extrapolation, the dose-response relationship is anticipated to remain linear. An interesting aspect of the peroneal MCV data is that all three exposed groups show responses that are less than the BMR of 10% change. The BMC is still obtained by extrapolating slightly outside of the range of the data, but, in this case, the extrapolation is to a higher concentration and effect level.

I.B.3. Uncertainty and Modifying Factors (Inhalation RfC)

UF — An uncertainty factor of 3 reflects extrapolation of human data to sensitive humans. A full uncertainty factor of 10 was not considered necessary based on concurrence with peer-reviewer comments, which indicated that the lack of metabolic activation as a precursor to toxicity and the mechanism of action (protein cross-linking in the axon) does not suggest any reason to expect differences in sensitivity. A factor of 10 is applied to account for both database deficiencies, including concern for possible developmental effects at low levels, and to extrapolate to a lifetime exposure.

MF — None

I.B.4. Additional Studies/Comments (Inhalation RfC)

The cross-sectional studies by NIOSH (1984) and Putz-Anderson et al. (1983) used the same exposed (n = 146) and nonexposed workers (n = 233) as did the Johnson et al. (1983) study. Exposure and companion groups and exposure levels are the same as those described for the Johnson et al. (1983) study. Historical exposures sampled from 1957 to 1978 averaged below 20 ppm (62 mg/cu.m), however brief periods of high excursions in carbon disulfide levels occurred occasionally. The exposure levels and groups were as described for the principal study. The authors examined a number of parameters in addition to those reported by Johnson et al. (1983), including cardiovascular status (clinical chemistries, ECG, and blood pressure), retinal abnormalities, CNS symptoms, psychological tests, endocrine and metabolic status (blood hormone levels and serum trace metals), and reproductive status (semen analysis and reproductive history). Results of these studies included significant increases in retinal microaneurysms and hemorrhages in exposed individuals compared with controls, but a concentration-related increase in response is not evident when analyzed by exposure category. In addition, an increased prevalence of blurred vision, memory difficulty, dizziness, insomnia, and fatigue was reported among carbon disulfide-exposed individuals. However, results of objective psychological and psychomotor tests do not corroborate the symptomatology. No effects were found in reaction time, visual acuity, visual search ability, or psychological or memory tests. No

exposure-related effects on other parameters were reported. These studies support the identification of the LOAEL from the Johnson et al. study and show possible CNS and ocular effects at the same level. The LOAEL is identified as discussed for the principal study.

Peripheral neuropathy was shown to result from long-term occupational exposure to carbon disulfide in a cross-sectional study of rayon workers exposed for 10.3 +/- 6.9 years (mean +/- SD, range 1-22 years; Hirata et al., 1984). Historical exposure estimates were based on area sampling between the years 1975 and 1981 (7430 samples; Sugimoto et al., 1981), but exposure monitoring prior to 1975 was not reported. Current exposure estimates were based on area sampling at the time of the study (275 samples at 24 locations) and personal samples (64 samples for eight job titles; Sugimoto et al., 1981). Personal samples were taken with a passive dosimeter; samples were collected on activated charcoal and analyzed by gas chromatography. The sampling time is not stated explicitly but is presumed to be 8 hours. The area sampling used approximately 1 L grab samples and spectrophotometric analysis. Current exposure estimates are based on the personal sampling results. The average exposure was 4.15 mg/cu.m (1.45 ppm) for the subjects examined by Hirata et al. (1984). The overall averages of all historical area samples is 19.5 mg/cu.m and, from current area samples, was 9.21 mg/cu.m. These results, coupled with the authors' statements that exposures were higher between 1961 and 1974, and that process and control improvements were made (unspecified), suggest that the current exposures measured by area and personal samples are not representative of exposures prior to the sampling program. Sugimoto et al. (1981) identified a cohort of 311 male and 65 female workers exposed to carbon disulfide; 205 male and 117 female workers from a textile machine manufacturing factory were used as the control group. Hirata et al. (1984) studied 70 exposed male workers and 70 age-matched controls selected randomly from the original cohort. Excluded from the study population were subjects with right arm trauma, diabetes, alcoholism, renal failure, neurological disease, and exposure to other toxic solvents. Besides age distribution and these exclusion criteria, no other information is given on the demographics of the control group. MCV and SCV were measured in the right ulnar nerve and normalized for skin temperature, although the room temperature in which the measurements were made was uncontrolled (range 22-31 C). Corrected MCV and conduction velocity of the slower motor fibers (CVSF) were found to be significantly lower in each age group of exposed vs. unexposed individuals ($p = 0.001$ for both parameters). Although compromised by the lack of information on earlier exposures and on the control group, the results are consistent with other occupationally exposed populations and show an effect at a lower concentration. A LOAEL of 1.45 ppm (4.52 mg/cu.m) is established in this study. The LOAEL(HEC), based on adjustment from an occupational study, is 1.61 mg/cu.m.

Ruijten et al. (1990) studied peripheral nerves, autonomic nerves, and color discrimination in male workers at a rayon plant. Control groups of 45 and 37 workers from the same plant were evaluated. The exposed and control groups were matched on a group basis for age, socioeconomic status, and nationality. Exposure levels were determined for various areas, based on personal samples (number of samples not reported) taken over a period of 3 years prior to the study. The results of a large number of area samples (number not reported) taken since 1946 indicated that exposure levels had not changed substantially (data not provided). Individual exposures were calculated based on time spent in various areas and were reported as a cumulative exposure. Average cumulative exposures for the exposed group was 165 ppm-months, and exposed workers were exposed for 20 +/- 9 years (mean +/- SD). The mean exposure was therefore 8.25 ppm (25.7 mg/cu.m). No other information is provided to characterize the exposure. Conduction velocity and refractory period of the peroneal and sural nerves were determined. Autonomic nerve function (heart rate variation during rest, deep breathing, and isometric muscle contraction) and color discrimination also were evaluated. A decrease in conduction velocity of the peroneal nerves and an increase in the refractory period were observed and were related to cumulative exposure. This study demonstrates a LOAEL for peripheral nervous system effects of 8.25 ppm [LOAEL(HEC) = 9.18 mg/cu.m, based on adjustment for an occupational exposure scenario]. This study is supportive of the LOAEL identified in the principal study but is not used as the basis of the RfC because of inadequate information on exposure characterization.

Sugimoto et al. (1984) studied cardiovascular effects and retinal effects in the cohort first described by Sugimoto et al. (1981) and used, in part, in the principal study (Hirata et al., 1984). No effects were found on blood pressure or blood cholesterol. The previously described carbon disulfide retinopathy, characterized by microaneurysms and small-dot hemorrhages, was not observed. These results suggest a NOAEL for retinal effects at the LOAEL for peripheral nerve effects that was identified in the principal study.

Cohorts of male workers from a Finnish viscose rayon plant exposed to carbon disulfide for 1-27 years were examined (n = 118) and compared with male paper mill workers not exposed to carbon disulfide (n = 100) (Seppalainen and Tolonen, 1974). Carbon disulfide levels in this cohort were fairly high and were estimated from historical records of air-sampling programs (Hernberg et al., 1970, 1976; Nurminen and Hernberg, 1985). Exposure levels in the viscose film factory and the carbon disulfide factory had not exceeded 20 ppm (62 mg/cu.m) since 1958, and, since 1962, the means were "mostly lower" than 10 ppm (31 mg/cu.m). In the rayon staple and rayon filament factories, the overall levels had been lower than 60 ppm (187 mg/cu.m) and, since 1960, lower than 30 ppm (93 mg/cu.m). Some of the exposed individuals had been removed from the carbon disulfide environment. Those still in contact with carbon disulfide (n = 65/118) had been exposed for 10-27 years (mean 19 years), whereas those who were removed (n = 53/118) had been exposed for 1-22 years (mean 12 years). Conduction velocities in the slower

motor fibers in the ulnar nerve (39.8 vs. 44.1 m/second, $p < 0.0005$) and the deep peroneal nerve (35.5 vs. 38.2 m/second, $p < 0.0005$) were the most significantly decreased by carbon disulfide exposure. There also were decreases in MCV of the tibial and peroneal nerves. In addition, the exposed group had a higher incidence of abnormal EEGs (21/54, compared with 6/50 in controls). No evidence of regression of the disorder after cessation of exposure was established. Increased cardiovascular-related mortality also was reported at 10-30 ppm carbon disulfide (31-93 mg/cu.m).

Peripheral nerve conduction velocity was measured in carbon disulfide workers suspected to have polyneuritis (n = 60) (Vasilescu, 1972). The concentration of carbon disulfide was approximately 5 ppm (15 mg/cu.m), but high excursion levels of 225 ppm (700 mg/cu.m) sometimes were reached. The limited information on exposure characterization in this study does not allow the estimation of a mean exposure. Conduction velocity was measured in the median, ulnar, and peroneal nerves and was found decreased in exposed individuals, even in those with no clinical signs. When exposed individuals were divided into two groups on the basis of the severity of their symptoms, it was found that the more severe polyneuropathy (decreased nerve conduction velocity, muscle pain, paresthesia, fatigue, and dizziness) was not reversed 1 year after termination of carbon disulfide exposure, whereas members of the second group (lower-limb paresthesia and decreased muscular power of limbs) recovered from their symptoms. The authors concluded that decreased nerve conduction velocity may be one of the early warning signs for carbon disulfide poisoning and could be used as an index of early carbon disulfide neuropathy. This study is not useful for quantitative assessment because individuals were selected for participation in this study on the basis of reduced nerve conduction velocity, and exposure levels were not characterized. In addition, there is no information on the control subjects used.

Clinical neurological examination of 16 men formerly exposed to a range of approximately 10 ppm (30 mg/cu.m) and 20 ppm (60 mg/cu.m) carbon disulfide for at least 10 years revealed abnormalities in 15 of the men (Aaserud et al., 1988, 1990). Cerebral computerized tomography scan revealed signs of atrophy in 13 men, and neuropsychological examination indicated brain organic changes in 14 men. There was no measurement of individual exposures, however, and no adjustment was made to account for other possible occupational exposure or for lifestyle factors.

Cirla et al. (1978) identified a cohort of rayon workers exposed to carbon disulfide. A total of 254 exposed workers were divided into six exposure categories based on historical area and personal monitoring data. Fifty-four workers who were employed in the same plant but in areas considered free of exposure were used as a comparison group. The comparison group is stated to be similar to the exposed group in personal and social characteristics, but no comparative demographic data are presented, and no data are presented on the exposure of the comparison group. It is stated that area samples were taken intermittently prior to 1960 and every 2 months

between 1960 and 1970, and personal sampling was adopted after 1970. Exposure categories are characterized in terms of the number of years worked, and the exposure concentrations are qualitatively described relative to the Italian maximum allowable concentration of 60 mg/cu.m. Sampling method, number of samples, and mean exposure levels for the groups are not provided. Gilioli et al. (1978) reported on the evaluation of neurological impairment in these workers. They performed neurological examinations, electroencephalography, ophthalmoscopy, and electromyographic measurements of nerve conduction velocity and latency of the peroneal nerve. Central and peripheral nervous system dysfunction (determined by neurological examination), retinal vascular changes, and reduced nerve conduction velocity were observed to increase with exposure. Limited statistical analyses are presented. The decrease in motor nerve conduction velocity showed significant effects using an analysis of variance, and individual t-tests showed significant differences between the comparison group and the moderately and heavily exposed groups, but not the light and very light groups. Retinal changes showed a significant trend from the light to heavy exposure groups, but individual comparisons were not made. This study shows a carbon disulfide-exposure-related effect on the retina and the peripheral nerves, but the lack of statistical analysis of the results, quantitative exposure information, and information on the comparison group make this study inadequate to form the basis of the RfC.

Cirla and Graziano (1981) examined a subset of the cohort identified by Cirla et al. (1978). The exposed group (n = 50) came from a single department and is a subset of the light-exposure group (n = 73) from Cirla et al. (1978), and the entire comparison group is used. Control individuals were evaluated for carbon disulfide exposure on the basis of working history and task evaluation; however, no measurements of background carbon disulfide concentration were performed for this group. Exposure period ranged from 3-12 years. Exposure levels are characterized in the text of the paper as approximately 20 mg/cu.m and always below 30 mg/cu.m, based on area sampling (number of samples and method not reported). The information available in one table suggests an overall mean exposure of approximately 10 mg/cu.m. Mean exposure levels are reported for eight job titles and range from 5-21 mg/cu.m, but it is not possible to calculate an overall mean exposure. In addition, individuals were paired according to sex, physical features, work shift, and smoking and alcohol-use history and were assumed to have similar socioeconomic status, diet, and education level. Measurement of peripheral nervous system function, among other tests, revealed that there was no difference in MCV, slow fiber conduction velocity, or residual latency of the peroneal nerve when exposed and control individuals were compared by Student's t-test. The clinical diagnosis of peripheral impairment was made for five exposed and two control individuals. No effect was found on psychological tests, including tests of intelligence, performance, and memory. This report suggests a NOAEL for peripheral nerve function of 10 mg/cu.m [NOAEL(HEC) = 3.57, based on adjustment from an occupational exposure scenario], but this value is not used in the RfC derivation because of inadequate quantitative exposure characterization in the study.

A study of two groups of viscose rayon production workers showed that decrements in nerve conduction velocity persisted 10 years after exposure ended in the most exposed group (Corsi et al., 1983).

In summary, several epidemiological studies of occupational exposures are available for carbon disulfide, which consistently point to peripheral neurotoxicity as a sensitive effect of long-term exposure in humans.

Laboratory animal studies on the neurotoxicity of carbon disulfide usually have been done in rats and provide histopathologic and neurochemical data that support neurotoxicity with carbon disulfide exposure. In general, however, concentrations used in these studies are considerably higher than the occupational exposures seen in epidemiological studies.

Male (10/group) and female (12/group) B6C3F1 mice, Fischer 344 rats (15/sex/group), and Sprague-Dawley rats (15/sex/group) were exposed to 0, 49, 297, or 798 ppm (0, 153, 925, or 2485 mg/cu.m, respectively) carbon disulfide for 6 hours/day, 5 days/week for 90 days (CIIT, 1983). Examination of high- dose mice revealed decreased erythrocyte counts, hemoglobin, hematocrit, serum protein, and brain weight; peripheral nerve degeneration; axonal swelling; nephropathy; mineralization and tubular epithelial syncytia of the kidney; and brown pigmentation of the spleen. In Fischer 344 rats exposed to 798 ppm (2485 mg/cu.m) carbon disulfide, there was an increase in iron-positive pigmentation of the spleen. Both sexes in the high-dose group and females in the 300-ppm group had axonal swelling of nerve fibers of the spinal cord and of muscular and sural nerves (teased fiber preparation). In addition, clumping and loss of myelin sheaths were observed. These changes were not observed in animals exposed to 297 ppm (925 mg/cu.m) carbon disulfide. High- dose Sprague-Dawley rats had ataxia (slight foot dragging), slight axonal swelling of ventral and lateral funiculi of the spinal cord, excess pigmentation of the spleen, and axonal swelling of muscular and sural nerves (teased fiber preparation). Details of the nerve morphology findings are reported by Gottfried et al. (1985). There was a decrease in absolute brain weight in both sexes at the high-dose level and in females at the mid-dose level. The LOAEL for neurotoxicity is 925 mg/cu.m [LOAEL(HEC) = 165 mg/cu.m] for rats and mice. No respiratory or ocular effects of carbon disulfide exposure were noted.

Rebert and Becker (1986) attempted to establish a dose response for peripheral nerve conduction time changes. Rats (10 females/group) were exposed to 0, 400, or 800 ppm carbon disulfide, 7 hours/day, 7 days/week for 11 weeks. In animals exposed to 800 ppm (2491 mg/cu.m), visual-evoked potentials and conduction time in peripheral nerves and brainstem auditory pathways were longer than in rats exposed to 400 ppm (1246 mg/cu.m). The potentials in the groups exposed to 400 ppm were longer than the controls, although the differences were not statistically

significant. The LOAEL for peripheral nervous system effects is 2491 mg/cu.m [LOAEL(HEC) = 726 mg/cu.m, based on dosimetric adjustment for an extrarespiratory effect of a gas].

Neurological effects such as hindlimb motor difficulties, reduced sciatic nerve conduction velocity, and degenerating nerve fibers were seen in rats exposed to 700 ppm (2180 mg/cu.m) carbon disulfide for 5 hours/day, 5 days/week for 12 weeks and observed for 18 weeks postexposure (Colombi et al., 1981). The decreased nerve conduction velocity (measured in 40 rats) was evident 3 weeks after the beginning of exposure (significance level and statistical test unspecified), and, by the ninth week of exposure, some animals showed slight clinical signs of neurological impairment, such as difficulty in standing and running. Morphological evaluation of the sciatic nerves at week 10 revealed slight alteration of the myelin sheaths and axonal swelling. These pathologies continued to progress until three weeks postexposure; however, they were slightly improved at the 6-week postexposure point and at all points in time thereafter, indicating that the neuropathy may have been reversible.

Sensory and motor function were measured in Long-Evans hooded rats (4 males/group) exposed to 5 or 12 weeks of 500 ppm (1557 mg/cu.m) carbon disulfide for 6 hours/day, 5 days/week, and compared with concurrent control animals (4 males/group) (Clerici and Fechter, 1991). Behavioral testing that utilized the acoustic startle reflex response was used in order to test acoustic and neuromuscular functioning before, during, and after exposure or control periods. Hearing function (sensory) was relatively unaffected by carbon disulfide exposure for either 5 or 12 weeks. However, mean amplitude of baseline startle responses decreased significantly after 5 weeks (48% decrease from control) and 12 weeks (66% decrease) of exposure, indicating neuromuscular damage. Partial recovery was seen on the fourth-week postexposure examination.

Saillenfait et al. (1989) exposed pregnant Sprague-Dawley rats (20- 23/group) to 0, 100, 200, 400, or 800 ppm (0, 311, 622, 1244, or 2488 mg/cu.m, respectively) carbon disulfide, 6 hours/day during gestational days 6-20. On day 21, maternal and fetal parameters were evaluated, including examination for external, visceral, and skeletal abnormalities. Chamber concentrations were stated to be within 5% of nominal, based on spectrophotometric analysis, but the number of samples was not given. Exposure to 400 or 800 ppm resulted in reduced maternal weight gain (19 and 48% reductions in the 400- and 800-ppm groups, respectively) and fetal body weight (6.6 and 22% in the 400- and 800- ppm groups, respectively). The number of litters examined was 40, 17, 17, 22, and 22 in the control and 100-, 200-, 400-, and 800-ppm groups, respectively. There were no effects on implantations, resorptions, live fetuses, or fetal sex ratio. Fetuses from animals in the 800-ppm exposure group had an increase in unossified sternebrae (16/289 vs. 3/558 in controls), an index of delayed fetal development. A slight increase in club foot at 400 and 800 ppm was noted (1/298 and 7/289 fetuses compared with 0/558 in controls) but was not statistically significant. No other effects were noted. A NOAEL of 400 ppm (1244 mg/cu.m) is established from this study for maternal and developmental effects.

The NOAEL(HEC) for developmental effects is 1244 mg/cu.m.

A developmental study was conducted using New Zealand White rabbits (PAI, 1991). In this study, rabbits (24/group) were exposed by inhalation to 0, 60, 100, 300, 600, or 1200 ppm (0, 187, 311, 934, 1868, or 3737 mg/cu.m, respectively) carbon disulfide, 6 hours/day on gestation days 6-18. Animals were evaluated on day 29. Maternal toxicity was observed as reduced body weight gain and adverse clinical signs (ataxia, lowered food consumption, or wheezing) in the 1200-ppm group, with some sporadic hematologic alterations at 600 ppm (e.g., decreased hematocrit on gestation day 19). These effects were not seen in an initial dosage range-finding study, where rabbits were exposed to 1000 ppm carbon disulfide. Embryotoxic effects (reduced mean fetal body weight, number of live fetuses, and postimplantation loss) were seen in the 600- and 1200-ppm exposure groups. In the group exposed to 1200 ppm, there were only seven litters with live fetuses, and there was a high incidence of developmental effects (increased cumulative skeletal and visceral malformations). In the other groups and controls, 20-23 litters were examined, and there were no significant increases in any gross, visceral, or skeletal abnormalities. Using dosimetric adjustment for an extrarespiratory effect, the NOAEL for developmental effects was 300 ppm [NOAEL(HEC) = 934 mg/cu.m], and the NOAEL for maternal toxicity was 600 ppm [NOAEL(HEC) = 1868 mg/cu.m].

In a developmental study performed for NIOSH [Beliles et al., 1980 (data also summarized in Hardin et al., 1981)], rabbits and rats were exposed to 0, 20, or 40 ppm (0, 62, or 125 mg/cu.m, respectively) carbon disulfide for 7 hours/day, 5 days/week for 3 weeks prior to mating. Following mating, groups of rats not exposed pregestationally were exposed to 20 or 40 ppm carbon disulfide on days 0-18 or days 6-18 of gestation, and rabbits were exposed to 20 or 40 ppm on days 0-21 or days 7-21 of gestation. Similarly, animals exposed pregestationally were divided into two groups that were exposed to the same concentration as used in the pregestational exposure and exposed during gestation days 0-18 or 6-18 (rats) or 0-21 or 7-21 (rabbits). Control animals were included that were unexposed during pregestational and gestation periods. Chamber concentrations were determined hourly, and the coefficient of variation of the chamber concentration ranged from 8-14%. In rats, there was no effect on maternal weight gain and no dose-related effect on maternal organ weights or histology of the liver or kidney. In 12-23 litters/group, there were no significant effects on uterine contents (early or late resorptions, number of fetuses, fetal weight, or fetal length), and no significant external, visceral, or skeletal malformations were observed. There was a slight but nonsignificant increase in resorptions and reduction in live fetuses in two groups (20 ppm, exposed during gestation, and 40 ppm, exposed pregestationally and during gestation). In the rabbit study there was a high level of mortality, which was not exposure related, and which makes interpretation of the rabbit study difficult. There was no effect on maternal body weight, organ weight, or histology of the liver or kidney. In 15-18 litters examined per group from the groups that were not exposed pregestationally, there was no effect on uterine contents and no increase in external, visceral, or skeletal abnormalities.

This study shows a NOAEL of 40 ppm for maternal and developmental toxicity for rats and rabbits and for exposures lasting throughout gestation or during the postimplantation period. The NOAEL (HEC) for developmental effects is 125 mg/cu.m.

In a developmental study of albino rats, 30-32 animals/group were exposed to carbon disulfide at concentrations of 0, 0.01, 3.20, 32.00, or 64.00 ppm (0, 0.03, 10.00, 100, or 200 mg/cu.m, respectively) for 8 hours/day throughout gestation (21 days) (Tabacova, 1989; Tabacova and Balabaeva, 1980; Tabacova et al., 1978, 1983). Some of the parental generation were examined prior to term, and some F1 animals were reared until maturity and mated within experimental groups to produce the F2 generation. The pregnant F1 females were exposed throughout gestation to the concentration of carbon disulfide to which they were exposed prenatally, including air-exposed controls. Status of the F1 and F2 generations was determined prenatally by gross examination of the uterine contents (no indication is given that visceral or skeletal malformations were examined) and several biochemical measurements. The F1 and F2 generations also were examined postnatally by examining growth, development, hexobarbital sleeping time, neurophysiologic parameters (motor coordination, open-field activity), weight gain, and survival. Some of these measurements were made on all exposure levels, and some are provided only for the two lowest concentration groups. In Tabacova et al. (1978), there also is a group exposed to 16 ppm (50 mg/cu.m), and some information is available, but this group is not included in the 1983 report, which is somewhat more detailed. The generation and measurement of the exposure atmosphere are described in Tabacova, 1989. The carbon disulfide levels were measured twice per day using a spectrophotometric method that has been used extensively (NIOSH, 1977), but has been replaced by gas chromatographic methods in the western literature since about 1970. No information is provided in any of the published reports on the purity of the test chemical or on the results of the chamber monitoring. The methods as described seem reasonable. The selection of the lowest exposure at a level that is 333 times lower than the next level was done to correspond to contemporary Bulgarian ambient (0.03 mg/cu.m) and occupational (10 mg/cu.m) standards. There is no information on whether the control groups were handled in the same way as the exposed groups, and no mention is made of the method of selection of mating pairs or whether sibling pairs were excluded in producing the F2 generation. It also is not clear whether the control group was run concurrently with the exposed groups. In the 1978 report, a control and three exposed groups (50, 100, and 200 mg/cu.m) are presented. In the 1983 report, the same data for the control and 100- and 200-mg/cu.m groups are presented with data from the two lower exposure levels. In another table, there are separate control groups reported for the 0.03- and 10.00-mg/cu.m groups and the 100- and 200-mg/cu.m groups. Despite these limitations, a variety of maternal and developmental effects were reported.

Maternal toxicity (reduced weight gain during gestation) was observed in the parental and F1 generations exposed to 100 mg/cu.m (F1 generation; 59% decrease was not reported as statistically significant) or 200 mg/cu.m carbon disulfide (27% in the parental generation and

74% in the F1 generation). For this endpoint, there are two control groups reported, and large differences between the control groups are unexplained. In contrast, Saillenfait et al. (1989) report no effect on maternal weight in rats exposed to 622 mg/cu.m and a 19% decrease at 1244 mg/cu.m. Average fetal weight is significantly decreased in this study at 100 and 200 mg/cu.m (5 and 7%, respectively). A 6.6% decrease in fetal weight was reported by Saillenfait at 1244 mg/cu.m, and no effect was observed at 622 mg/cu.m. However, the Saillenfait et al. (1989) study exposed for only 6 hours/day, starting at day 6, compared with 8 hours/day throughout gestation in Tabacova's studies; this difference could account for the difference in results. Significantly increased preimplantation lethality at 200 mg/cu.m and a slight increase at 100 mg/cu.m indicate adverse developmental effects at these levels (Tabacova et al., 1978). In the only other study to include exposure throughout gestation, Beliles et al. (1980) report no preimplantation loss at concentrations up to 125 mg/cu.m.

Malformations reported by Tabacova et al. (1983) include a significant increase in clubbed foot and hydrocephaly in the 100 and 200 mg/cu.m animals and increased hypognathia and tail malformations at 200 mg/cu.m. In the Saillenfait study, a nonsignificant increase in clubbed foot was observed at 2488 mg/cu.m, but no other malformations were observed. The fact that the effects seen by Tabacova were not seen at 25-fold higher concentrations in the later study could be explained by the exposure during the first 6 days of gestation in the Tabacova studies. The Beliles study did not see these effects at 125 mg/cu.m, a result that may not be inconsistent with the Tabacova data, because different rat strains were used. It is a concern that the gross effects reported by Tabacova were not seen in the F1 generation animals that were delivered and studied postnatally (hydrocephalus, clubbed foot, and tail malformation should have been visible in the surviving animals). No malformations were observed in the F1 animals or maternal weight changes in the parental generation exposed to 0.03 or 10.00 mg/cu.m. No information on fetal weight preterm or postnatal weight changes are reported for the two lower dose levels. There is, therefore, no reported evidence of prenatal developmental effects in the F1 generation exposed to 0.03 or 10.00 mg/cu.m. When pregnant F1 females were exposed during gestation, evidence of more severe maternal and developmental effects were observed. These effects included greater maternal weight loss during gestation in the 200 mg/cu.m- group (a larger reduction in weight than parental generation at the same exposure level) and increased incidence and severity of malformations compared with the previous generation. Increased malformations also occurred at lower concentrations (0.03 and 10.00 mg/cu.m), which did not affect the F1 generation. This effect was explained by the authors as intrauterine sensitization, a mechanism by which exposure of the parental generation resulted in an F1 generation that was more sensitive to the developmental effects of carbon disulfide during pregnancy.

A variety of observations and measurements were made to evaluate postnatal development in F1 and F2 pups. Decreased postnatal survival at 200 mg/cu.m and decreased postnatal weight gain on days 4 and 7 was observed in animals exposed to 100 or 200 mg/cu.m carbon disulfide

(Tabacova et al., 1978). Tabacova and Balabaeva (1980) report postnatal examination of animals exposed to 0.03 or 10.00 mg/cu.m. A decrease in viability at postnatal day 21 was significant, but this effect is not seen in animals exposed to 50 or 100 mg/cu.m (Tabacova et al., 1978). Postnatal observations show significant effects on eye opening (day 18), auditory startle reflex (day 14), visual placing response (day 18), and righting behavior at 10 mg/cu.m (Tabacova and Balabaeva, 1980; also reported in Tabacova and Hinkova, 1979). These responses were reported for single times postnatally and were normal at an unspecified later time. No other studies of postnatal development after exposure to carbon disulfide are available. Other parameters measured postnatally in this study (Tabacova et al., 1983) include hexobarbital sleeping time and neurophysiological tests (narrow-path crossing and open- field activity). Hexobarbital sleeping time is increased significantly in F1 and F2 animals exposed to 10 mg/cu.m (not reported for higher concentrations) at 7 and 14 days but not at 21 days of age. Because this measurement was made on only 6-8 pups/group, and the controls are variable, it is not considered a clear indication of a developmental effect. Narrow-path crossing is a measure of motor coordination. No effect is seen in F1 animals exposed to 0.03 or 10.00 mg/cu.m. In exposed F2 animals, a significant decrement in this behavior was observed as a decrease in mean distance covered in groups exposed to 0.03 or 10.00 mg/cu.m. This response shows no concentration-response relationship because the exposures differ by 300-fold, and the responses are identical, and the parameter is not reported for other exposure concentrations. Narrow-path crossing also is reported as number of slips and falls, both of which increase at 10 mg/cu.m, but are not reported at higher concentrations. Open-field motor activity is reported as the number of squares crossed, the number of rearings, and gait defects. The number of squares crossed was increased at day 14 and decreased at day 21 in F1 groups at 0.03 and 10.00 mg/cu.m; it was unchanged at day 14 and decreased at day 21 in F2 animals at 0.03 and 10.00 mg/cu.m. The number of rearings is unchanged in F1 animals and decreased in F2 animals at 0.03 and 10.00 mg/cu.m (response at 0.03 mg/cu.m was slightly greater than at 10). The percent with gait defects is increased in F1 animals at 10.00 mg/cu.m and in F2 animals at 0.03 and 10.00 mg/cu.m and shows a reasonable concentration response. The criteria for identifying a gait defect is not discussed, so the adversity of this response is unknown. Fifty and 75% increases in open-field motor activity were reported for the 0.03- and 10.00-mg/cu.m groups, respectively (Tabacova and Balabaeva, 1980). This result is not quantitatively consistent with the slight increases in the open-field parameters reported in Tabacova et al., 1983, but it is not clear whether the same parameter is reported in the two studies.

In summary, this study shows a variety of developmental effects of low- level carbon disulfide exposure that are difficult to interpret due to poor reporting of experimental design details and results. The effects measured postnatally, including morphological, sensory, and behavioral endpoints, are limited because they are reported for only two exposure levels. The endpoints which are affected at both lower concentrations do not show reasonable concentration-response behavior, and the ones affected only at 10 mg/cu.m are not supported by other data at higher

exposure concentrations. Nevertheless, a variety of endpoints are shown to be significantly changed at 10 mg/cu.m. The effects on preimplantation losses at 100 and 200 mg/cu.m are the strongest data in these studies; the slight inconsistency with the Beliles study could be due to strain differences. The increase in malformations in the F1 and F2 generations seems compelling due to the increase in incidence and severity with concentration and between the F1 and F2 generations. The slight inconsistency with the Beliles study (no effect at 125 mg/cu.m, compared with an effect at 100 mg/cu.m) could be explained by strain differences. The lack of effect in the Saillenfait study at a 25-fold higher concentration could be explained by strain differences or differences in protocol (exposure throughout gestation vs. exposure on days 6-18). The dramatic increase in response in the F2 generation indicates clearly adverse effects at concentrations as low as 0.03 mg/cu.m. This experimental design has not been duplicated, so no data are available for direct comparison. The more recent developmental studies use a more typical protocol and cannot address directly the effects in the F2 generation, although there is little agreement among these studies where they look at the same or similar parameters. Although the effects at 0.03 and 10.00 mg/cu.m in the Tabacova studies cannot be refuted, there are substantial issues affecting interpretation that cannot be resolved. These studies clearly define a LOAEL of 100 mg/cu.m for maternal and developmental effects. A LOAEL for developmental effects at 10 mg/cu.m, including malformations in the F2 generation and postnatal morphological development and postnatal behavior in F1 and F2 generations is identified by these studies but is not strongly supported by other data. The effects reported at 0.03 mg/cu.m are not considered to be useful because the effects are of questionable significance and do not show reasonable dose-response behavior, and because of questions regarding the ability to measure such low levels.

The BMC analysis was performed for the developmental effects using the models of ICF Kaiser (1990a,b), which were run with and without a threshold parameter and with no background parameter, because the incidence of effects in the control groups was zero. The specific developmental models were not used because software was not available, and because individual litter data were not available for these studies. The BMC was calculated from the data from Tabacova et al. (1978) on total malformations and hydrocephalus in the F2 generation and for the data on external malformations from Tabacova et al. (1978). Based on the results from these analyses, the BMC from the data on total malformations from Tabacova et al. (1983) result in the lowest BMC for the developmental data sets. The fit to the points is poor, based on the chi-square test. Because of the limitations of this data, the BMC is presented for comparison but is not recommended for derivation of the RfC. The most appropriate BMC from the developmental data is from the total malformation from Tabacova et al. (1983) (18.7 mg/cu.m). The benchmark concentration was based on a response of 10% in total malformations using an extra risk model.

In humans, vascular atherosclerotic changes are a primary effect following long-term exposure to carbon disulfide. This is supported by epidemiological studies that have established a relationship between occupational exposure to carbon disulfide and increased mortality due to

coronary heart disease. However, since reliable retrospective data on exposure levels are not available, it is impossible to establish a dose-response relationship or a NOAEL. In addition, coronary heart disease has a multicausal origin that is influenced by a large number of other risk factors, such as smoking, dietary habits, diabetes, and physical inactivity.

A retrospective mortality study of 223 viscose rayon workers employed for more than 10 years and who were exposed to carbon disulfide levels above 20 ppm (62 mg/cu.m) revealed a statistically significant increase (2.5-fold) in cardiovascular mortality, as compared with 174 controls from the same factory (Tiller et al., 1968). Over the 30-year study period, 42% of all deaths in rayon process workers were attributed to coronary heart disease; the proportion was 24% for other rayon workers and 17% for other local males used as controls. The excess mortality was more pronounced in the 1940s and declined towards 1960, indicating a strong dependence on the intensity of exposure, which had decreased during this interval. The same study demonstrated that the death rate from coronary heart disease was proportionally higher among workers engaged in the viscose spinning process than in other workers. Nonexposed workers also had a significantly higher death rate than expected for coronary heart disease, as did controls not employed in the viscose industry; these factors limit the value of this study. Other limitations include an inappropriately selected control group, failure to control for other coronary heart disease risk factors, such as smoking, dietary habits, physical inactivity, and obesity and failure to monitor blood pressure and blood lipid levels. In addition, there may have been concomitant exposures to other chemicals in these industrial environments.

A prospective mortality study at a Finnish plant from 1967-1977 revealed a similar excess of deaths (2.5-fold) due to coronary heart disease (Tolonen et al., 1979). Two cohorts were followed over a 10-year period; 343 viscose rayon workers exposed to carbon disulfide were individually matched with workers from a local paper mill. There was no significant difference between the exposed and control groups with regard to smoking habits, physical activity, obesity, or drug treatment. Atmospheric carbon disulfide concentrations were 10-30 ppm during the 1960s, 20-60 ppm during the 1950s, and higher in earlier time periods. The increase in deaths due to coronary heart disease was 29 in the exposed group versus 11 in the control group. Periodic health surveys during the study revealed increased incidence of angina and increased blood pressure, as compared with a well-matched control group. The incidence of deaths from coronary heart disease appeared to be much greater during the first 5 years, as reported in interim results of the same cohorts, but the numbers were too small to support any conclusions (Hernberg et al., 1970).

Among men who had been exposed to carbon disulfide for 5 or more years between 1942 and 1967, the incidence of angina in the exposed workers was 25%, as compared with 13% in controls, and a significant increase in blood pressure was seen (Hernberg et al., 1973, 1976; Tolonen et al., 1975). Nonfatal first cardiac infarctions were more frequent in the exposed group

(11) than in the control group (4). The relative risk of a fatal myocardial infarction was 4.8 times greater among those exposed to carbon disulfide; 16/343 men died of coronary heart disease within the 5-year period, in comparison to 3/343 men in the control group ($p < 0.007$) (Hernberg et al., 1973; Tolonen et al., 1975). In a subsequent study, the original relative-risk estimates were adjusted for potential confounding effects of hypertension and aging. After these adjustments, carbon disulfide exposure yielded a relative risk of 2.3 for coronary disease mortality (Nurminen et al., 1982). Thus, although the prognosis of exposed workers improved with improved occupational hygienic standards and with a reduction in the length of exposure over a lifetime, there is apparently some increased risk attributable to carbon disulfide exposure in this cohort. However, there were no adjustments for possible concomitant exposures to other chemicals.

I.B.5. Confidence in the Inhalation RfC

Study — Medium
Database — Medium
RfC — Medium

Confidence in the principal study (Johnson et al., 1983) is medium. The study is well designed and conducted, uses adequate numbers of subjects, and is well supported by other occupational studies examining the same effect; however, considerable uncertainty exists regarding the exposure histories of the cohorts examined. A considerable number of well-conducted occupational studies have defined the effects of carbon disulfide in humans; however, a significant question remains regarding the possibility of developmental effects in humans. Confidence in the database, therefore, is medium. Accordingly, confidence in the RfC is medium.

I.B.6. EPA Documentation and Review of the Inhalation RfC

Source Document — This assessment is not presented in any existing U.S. EPA document.

This assessment was peer reviewed by external scientists. This review was completed on 05/22/1995. Their comments have been carefully evaluated and considered in the revision and finalization of this IRIS Summary. A record of these comments is included in the IRIS documentation files.

Other EPA Documentation — U.S. EPA, 1986

Agency Work Group Review — 01/19/1989, 02/16/1989, 03/21/1989, 08/15/1991, 12/11/1991, 05/10/1995

Verification Date — 05/10/1995

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfC for Carbon disulfide conducted in September 2002 identified one or more significant new studies. IRIS users may request the references for those studies from the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

I.B.7. EPA Contacts (Inhalation RfC)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Carbon disulfide
CASRN — 75-15-0

This substance/agent has not undergone a complete evaluation and determination under US EPA's IRIS program for evidence of human carcinogenic potential.

III. [reserved]
IV. [reserved]
V. [reserved]

VI. Bibliography

Substance Name — Carbon disulfide
CASRN — 75-15-0

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VI.C. Carcinogenicity Assessment References

None

VII. Revision History

Substance Name — Carbon disulfide
CASRN — 75-15-0

Date	Section	Description
08/01/1995	I.B.	Inhalation RfC summary on-line
12/03/2002	I.A.6., I.B.6.	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — Carbon disulfide
CASRN — 75-15-0
Last Revised — 09/30/1987

- 75-15-0
- CARBON BISULFIDE
- CARBON BISULPHIDE
- Carbon Disulfide
- CARBON DISULPHIDE
- CARBONE (SUFURE DE)
- CARBONIO (SOLFURO DI)
- CARBON SULFIDE
- CARBON SULPHIDE
- DITHIOCARBONIC ANHYDRIDE
- KOHLENDISULFID (SCHWEFELKOHLENSTOFF)
- KOOLSTOFDISULFIDE (ZWAVELKOOLSTOF)
- NCI-C04591
- RCRA WASTE NUMBER P022
- SCHWEFELKOHLENSTOFF
- SOLFURO di CARBONIO
- SULPHOCARBONIC ANHYDRIDE

- UN 1131
- WEEVILTOX
- WEGLA DWUSIARCZEK