MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

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INTEROFFICE COMMUNICATION

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August 23, 1999

TO: File for Gamma-butyrolactone (CAS No. 96-48-0)

FROM: Michael Depa, Air Quality Division, Toxics Unit

SUBJECT: Screening Level Determination

The initial threshold screening level (ITSL) for gamma-butyrolactone (GBL) is 280 µg/m³ (24-hour average).

The following references or databases were searched to identify data to determine the screening level: U.S. EPA Integrated Risk Information System (IRIS), Registry for Toxic Effects of Chemical Substances (RTECS), American Conference of Governmental and Industrial Hygienists (ACGIH) Threshold Limit Values (TLVs), National Institute for Occupational Safety and Health (NIOSH) Pocket Guide to Hazardous Chemicals, Environmental Protection Bureau Library, International Agency for Research on Cancer (IARC) Monographs, Chemical Abstract Service (CAS) Online (1967- August 4, 1998), National Library of Medicine (NLM), Health Effects Assessment Summary Tables (HEAST), and National Toxicology Program (NTP) Status Report. The EPA has not established a reference dose (RfD) or a reference concentration (RfC) for GBL. There are no occupational exposure limits for GBL.

Background Information

The molecular weight of GBL is 86.1g. GBL is completely miscible in water (IARC, 1976). The density of GBL is 1.144 g/ml. GBL undergoes the reactions of other gamma-lactones such as ring openings and reactions in which oxygen is replaced by another ring hereroatom. It is rapidly hydrolyzed by bases and slowly hydrolyzed by acids (NTP, 1992). GBL and its hydrolytic product, γ-hydroxybutyrate (GHB), have been used in humans as anesthetic agents or anesthetic adjuvants due to their sedative-hypnotic effects (NTP, 1992).

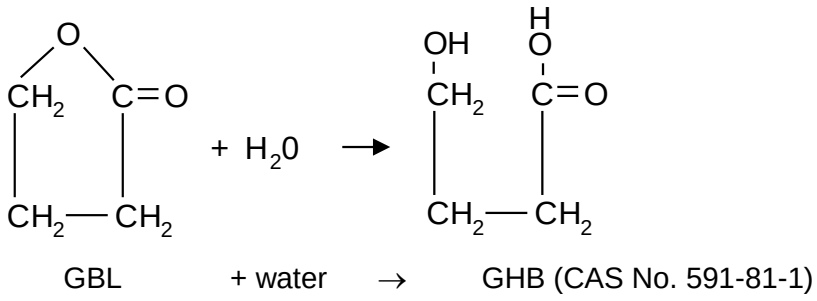

Figure 1. Hydrolysis of Gamma-Butyrolactone (GBL) to Gamma-Hydroxybutyrate (GHB)

GBL was found in the brains of rats at a concentration of 200 pmol per gram of tissue (Snead et al., 1989). GHB (gamma-hydroxybutyrate) is the principal metabolite of GBL in mammals, and is also thought to occur naturally in the brains of mammals (NTP, 1992). Although GBL rapidly converts to GHB in vivo, when equalmolar doses of GBL and GHB were compared both parenterally and orally in rats, GBL gave a more prolonged hypnotic effect (Lettieri et al., 1978). Lettieri et al., (1978) stated, "In

spite of the rapid metabolism of GBL to GHB, the apparent tissue distribution of these two compounds may be different." This may indicate that GBL is a more potent sedative than GHB. In contrast, when petit mal seizures induced by GBL and GHB were treated with other seizure producing stimuli (e.g., pentyleneterrazole, systemic penicillin and photic stimulation), all lowered the threshold to GHB induced seizure, bit did not interfere with the brain kinetics of animals treated with GBL (Snead, 1988). In any case, it appears that a direct comparison of toxicity between these compounds can not be made. Nonetheless, there are some important similarities.

Both GBL and GHB have been extensively investigated as a tool for inducing petit mal (absence) seizures. Experiments in rats with GHB have shown that GHB induced seizures are enhanced by the administration of a structurally similar compound called gamma-aminobutyric acid of GABA (Snead, 1990). GABA is one of the human brain's major inhibitory neurotransmitters (dopamine agonist), being released at 30% of its synapses (Voet et al., 1990). GHB specific receptors have been found in human and rat brains (Snead et al., 1984). Furthermore, incubated rat brain slices metabolized GHB to GABA (Vayer et al., 1984). Within the CNS, GHB mediates sleep cycles, temperature regulation, cerebral glucose metabolism, blood flow, memory, and emotional control (Li et al., 1998a). Research on the neurological effects of GHB have recently focused on its use in the treatment of opioid and alcohol withdrawal symptoms.

GHB is also used as an illicit drug and is "marketed" as a growth-hormone releaser for bodybuilders. Chin et al., (1992) reported a series of 5 representative patients in California who experienced adverse reactions from the ingestion of GHB. The most commonly reported symptoms included abrupt drowsiness, dizziness, and a "high." Other effects were headache, nausea, vomiting, myoclonic jerking, and short-term coma. Chin et al (1992) also stated that there have been no reported deaths due to GHB ingestion.

Clinical Effects in Humans

A report was identified in which two cases of GBL poisoning were summarized (Rambourg-Schepens et al. 1997). **CASE 1:** a 27-year old man with no significant past medical history intentionally ingested 100 mL of nail polish remover equivalent to 71 mL pure GBL. The other ingredients consisted of lanolin, water, dye and fragrance. About 45 minutes after ingestion, he became comatose and was admitted to a hospital where he was endotracheally intubated. Because his respiration was quick and shallow mechanical ventilation was started. He was transferred to intensive care unit in a deep coma, unresponsive to painful stimuli and his pupils were not reactive to light. He had an abnormal EKG and a heart rate of 55 bpm. Blood and urine toxicological screening was negative for alcohol, benzodiazepines, carbamates, barbiturates and tricyclic antidepressants. A chest radiograph showed no infiltrates. He woke up 5 hours after ingestion and was confused and agitated, necessitating weaning from mechanical ventilation. Eight hours after ingestion he displayed a normal EKG and heart rate. Nine hours after ingestion he was fully awake and orientated with no memory about what happened the previous day. The dosage in mg GBL per kg body weight was calculated to be 1160 mg/kg (assuming a body weight of 70 kg). **CASE 2:** A 14-month-old boy ingested an unknown amount of a nail polish remover (the same product and in CASE 1). He was discovered shortly after ingestion, and after induction of vomiting was attempted by his family he rapidly became cyanotic and hypertonic. About 1 hour later he was admitted to a local hospital. Neurologic examination revealed the patient was flaccid and responsive to painful stimuli. His pupils were miotic and unreactive. Upon admission to the ICU 3 hour after ingestion, the patient was still comatose, hypertonic and unresponsive to pain. Heart rate was 100 bpm, blood pressure 100/80 and respiratory frequency 20/min. Biological values were within normal limits. Approximately 5 hours after ingestion, the patient had a sudden significant improvement in consciousness but was still confused. About 8 hours after ingestion the patient was fully awake and he was discharged from the hospital the following day. The authors stated that the clinical course observed with GBL looks very similar to gamma hydroxybutyric acid (GHB), which is used as an anesthetic. The authors suggested that GBL is partially hydrolyzed to GHB, thus accounting for the clinical features, and then further metabolized to succinic acid explaining the acid pH of the urine seen in the first patient.

In a double-blind clinical study of eight opioid-dependent patients, Rosen et al. (1997) found subjects given oral doses of 30 mg GHB per kg body weight rated “sluggish,” “spaced,” “carefree,” and “good-mood” higher than subjects given a placebo. At a dose of 15 mg/kg GHB, 5 out of 8 patients rated the medication as “most like a placebo.” The neurological effects identified at the 30 mg/kg dose were deemed to be an acute lowest-observed-effect-level (LOEL). The 15 mg/kg dose was determined to be a no-observable-effect-level (NOEL).

In another human clinical study (Gallimberti et al, 1989), subjects with alcohol withdrawal syndrome were given 50 mg/kg which led to a “prompt reduction in withdrawal symptoms, such as tremors, sweating, nausea, depression, anxiety, and restlessness” with the only side-effect being “dizziness.” The same researchers performed a 3-month double blind clinical study (Gallimberti et al., 1992) where they administered GHB orally at 50 mg/kg divided into three daily doses for the first 3 days then weekly for the next 3 months. Adverse side effects were investigated using a standard questionnaire. Four of the 36 GHB treated subjects and on of the 35 placebo subjects complained of dizziness and vertigo after the fist morning dose on the first three days of treatment. The symptomatology was transient, disappearing within 6 hours. Two patients on GHB and one on placebo complained of headache after the fist morning dosage persisting for 3 to 4 hours. This symptomatology disappeared following the 3rd day of treatment. No patient showed alterations in the renal blood and liver tests. Blood pressure and pulse rate did not change significantly during the 3-month treatment period. Gallimberti et al. (1994) also examined the efficacy of GHB in the treatment of opiate withdrawal in two patients (50 mg/kg divided into 3 daily doses for three days then weekly for three months) and found good tolerability with no clinical phenomena interpreted as GHB side effects.

To test its effects on sleep, GHB was administered in a single oral dose to three groups of four patients at 50, 74 or 100 mg/kg (Hoes et al., 1980). The 75 mg/kg dose groups was administrated GHB for on night. The 50 and 100 mg/kg dose groups received GHB one hour before bedtime on four consecutive nights. Sleep induction was rapid and irresistible for the 75 and 100 mg/kg dose groups. At the 100 mg/kg dose level, all 4 patients suddenly awoke 4-5 hours after administration of GHB when the plasma levels of GHB were 90 µg/ml, after which they slept again. After 8 hours, GHB had virtually been eliminated from the blood. The authors stated that the patients awoke freshly in the morning. They stated that th mood parameters (vitality, appetite and hangover effect) were surprisingly good.

In a pharmacokinetics study, sixteen male patients with biopsy-proven cirrhosis were administered a single oral dose of 25 g/kg GHB (Ferrara et al., 1996). Compared to those previously determined in eight healthy control subjects given the same GHB dose, mean Area Under the Curve values were double or greater in the cirrhotic patients. Terminal half-life was significantly longer in nonascitic patients than in control subjects (32 vs. 22 minutes). Nonetheless, GHB plasma concentrations fell to either undetectable or negligible levels by the end of the usual dosing intervals (6-8 hrs.).

In a report of patients with GHB ingestion confirmed by urine mass spectrometry admitted to a high volume urban emergency department, a patient presenting with combination substance abuse involving GHB was observed in what the authors called a “peculiar state of violent aggression…despite near or total apnea” (Li et al., 1998b).

Genetic Toxicology

The NTP (1992) tested GBL for induction of gene mutations in Salmonella typhimuruim strains (TA100, TA1535, TA1537, and TA98). No significant increase in mutant colonies was seen. Also no induction of sex-linked recessive lethal mutation in germ cells of male *Drosophila melanogaster* was observed following exposure of adult males to GBL by feeding (20,000 or 28,000 ppm) or by injection (15,000 ppm). In cytogenetic tests with CHO cells GBL induced SCE and Abs endpoint was elevated in the absence of S9. In the SCE test, concentrations of 3,010 to 5,010 µg/ml yielded positive results. In the Abs test, GBL caused significant increases in aberrations.

Animal Studies

Groups of 13 or 14 male Wistar rats (21 days old) were dosed in drinking water with 0, 365 or 730 mg GBL per kg body weight (0, 0.5 or 1% by volume) for approximately 20 days (Debeljuk et al., 1983). There was no difference between dosed and control rats in body weight, serum prolactin levels or seminal vesicle weight. However, testicular weight was significantly decreased in the dosed rats compared to controls ($p<0.01$). A LOAEL of 365 mg/kg was identified from this study.

Groups of 5 male and female F344/N rats were gavaged with 0, 75, 150, 300, 600 or 1200 mg/kg GBL for 5 days per week for 16 days (NTP, 1992). All male and female rats receiving 1200 mg/kg GBL died within the first three days of the study; one male rat receiving 600 mg/kg died on day 3. There were no significant differences between the final mean body weights of dosed animals compared to controls. The mean body weight gains of females given 300 mg/kg or less and of all the males given GBL were similar to those of the controls. The body weight gain of the female rats in the 600 mg/kg dose group was statistically lower ($P<0.01$) than controls.

Groups of 5 male and female B6C3F1 mice were gavaged with 0, 87, 175, 360, 700 or 1400 mg/kg of GBL for 5 days per week for 15 days (NTP, 1992). All male mice and 4 female mice receiving 1400 mg/kg GBL died from chemical toxicity before the end of the study. Mean body weight and weight gains were similar to controls. Mice receiving doses of 350 mg/kg or more became recumbent or inactive shortly after dosing. Some mice also exhibited irregular respiration or dyspnea.

Groups of 10 male and female F344/N rats were gavaged with 0, 56, 112, 225, 450 or 900 mg/kg GBL for 5 days a week for 13 weeks (NTP, 1992). All male rats in the 900 mg/kg dose group died by the 6th week. There were no other statistically significant decreases in survival in any of the other groups of rats. Final body weight and weight gain was decreased in the males dosed with 450 mg/kg when compared to controls. Rats in the 225 and 450 mg/kg dose groups exhibited slight inactivity after dosing. After 2 to 3 weeks, all animals ceased to react visibly to the daily administration of GBL, indicating some form of adaptation or tolerance to its “anesthetic” and sedative properties. At necropsy there were no biologically significant differences in absolute or relative organ weights between dosed and control rats, and no lesions were attributed to GBL administration. Microscopic examination of tissue specimens revealed increased incidences of inflammation of the nasal mucosa in dosed rats. Similar lesions have been seen in other gavage studies with a variety of chemicals and may be related to the reflux of the gavage solution into the nasopharynx after dosing.

Groups of 10 male and female B6C3F1 mice were gavaged with 0, 65, 131, 262, 525 or 1050 mg/kg GBL for 5 days a week for 13 weeks (NTP, 1992). Survival of dosed animals was similar to controls. The final body weight and weight gain of the male mice dosed with 1050 mg/kg were statistically lower than controls. Mice in the 525 and 1050 mg/kg dose groups were recumbent several minutes after dosing, but were normal at the next observation period several hours later. Mice given 262 mg/kg exhibited moderate inactivity after dosing. There were no biologically significant differences in relative or absolute organ weighs between dosed and control mice. No gross or microscopic lesions related to GBL were observed.

In a chronic bioassay, groups of 50 male and female F344/N rats and B6C3F1 mice were dosed by gavage with GBL for 5 days a week for 2 years (NTP, 1992). The doses administered to groups of 50 animals per sex were 0, 112 and 225 mg/kg for male rats; 0, 225 and 450 mg/kg for female rats; 0, 262 and 525 mg/kg for male and female mice. **RATS:** The mean body weight of male rats were similar to those of the controls throughout the study. The mean body weight of high-dose female rats was lower than that of the controls after week 5 and was 10% to 20% lower than that of controls throughout the second year. The survival of dosed male and female rats was similar to that of controls. No increased incidence of neoplasms or nonneoplastic lesions in male or female rats were related to the administration of GBL. **MICE:** The final mean body weights of low- and high-dosed male mice were 6% lower than that of the controls. Mean body weights of female mice in the low and high dose groups were 17 and 14% lower than controls, respectively. The survival in high-dose male mice was

significantly lower than that of the controls, primarily due to injuries resulting from fighting. Concerning the fighting the NTP stated

> The increased aggression seemed to be related to the sedative or anesthetic properties of γ-butyrolactone. High-dose male mice were noted to be partially sedated or lethargic and inactive after dosing. The first males to recover were observed to attack and bite those male mice still sedated. Bite wounds, scratches, and sores around the genitalia and backs of the mice were more frequently observed in the low- and high-dose mice as were a number of nonneoplastic lesions believed to be related to debilitation, stress, or ascending infections of the urogenital tract as a result of the fighting.

In male mice statistically increased incidences of these lesions occurred: chronic inflammation of the skin, skin ulcers, thymus depletion, thymus epithelial hyperplasia, lung hemorrhage, and inguinal lymph node hyperplasia. Even though these lesions were all statistically increased compared to control mice, the NTP stated that these, "nonneoplastic lesions in male mice were considered to be associated with fighting and bite wounds." The NTP concluded that "There were no nonneoplastic degenerative lesions associated with the administration of GBL to male or female mice for up to 2 years." The survival of dosed female mice was similar to that of the controls. Concerning carcinogenic effects, increased incidences of proliferative lesions primarily hyperplasia of the adrenal medulla in low-dose male mice were associated with GBL (benign or malignant pheochromocytoma in control, low dose and high dose male mice: 2/48, 6/50, 1/50; hyperplasia: 2/48, 9/50, 4/50). **SUMMARY of NTP CONCLUSIONS:** Under the conditions to these 2-year gavage studies, there was no evidence of carcinogenic activity of GBL in male or female rats. There was equivocal evidence of carcinogenic activity of GBL in male mice based on marginally increased incidences of adrenal medulla pheochromocytomas and hyperplasia in the low-dose group. The sensitivity of the male mouse group to detect carcinogenesis was reduced by the low survival of the high-dose group associated with fighting. There was no evidence of carcinogenic activity of GBL in female mice. The nonneoplastic effects of GBL are summarized in Table 1.

Table 1. Effects of GBL Observed by the NTP (1992): Chronic Gavage Studies

Sex and Species **Low and High Doses**	**Body Weight** (low and high dose relative to controls)	**Survival** (low and high dose relative to controls)	**Nonneoplastic Lesions** (low and high dose relative to controls	**Neurological Effects** (low and high dose respectively)
Male Rats **112 and 225 mg/kg**	NE, NE	NE, NE	NE, NE	NE, sedative effects*
Female Rats **225 and 450 mg/kg**	NE, ↓	NE, NE	NE, NE	NE?, NE? (not mentioned in text)
Male Mice **262 and 525 mg/kg**	NE, NE	NE, ↓	↑, ↑	Increased aggression at both doses
Female Mice **262 and 525 mg/kg**	↓, ↓	NE, NE	NE, NE	NE?, NE? (not mentioned in text)

NE = No Effect
* 13-week study

In a teratogenicity study, groups of 10 pregnant outbred Sprague-Dawley rats were dosed by gavage with 0, 10, 50, 125, 250, or 500 mg GBL per kg body weight on gestation days 6 through 15 (Kronevi et al, 1988). There was no significant difference in maternal body weight, or food and water consumption compared to controls. No differences were found between the controls groups and the treated groups with regards corpora lutea, total implantation sites, alive and dead fetuses, resorptions, preimplantation and postimplantation losses, or male/female ratios. After internal examination of the soft tissues under the dissection microscope, no abnormalities were observed in any fetus. Examination of the fetuses for skeletal alteration revealed an increase incidence of unossified hyoid cartilage in the 10 and 125 mg/kg dose groups. A significant decrease in placental weight was observed in all dosed groups

compared to controls. The authors stated that, “The skeletal alterations observed seemed not to appear in a systematic manner and are thus not considered to be due to GBL exposure.” The authors also stated that the relationship between GBL exposure and an increase in fetal weight could not be explained.

In an acute inhalation study, one group of 5 male and 5 female Sprague-Dawley rats received a single 4-hour exposure to GBL (Monsanto, 1991). The mean exposure concentration was 5.1 mg/l in air. A 14-day observation period followed the exposure during which there were no moralities. Immediately after the exposure, notable observations included: shallow breathing and hypoactivity. At the end of the 14-day observation period, gross necropsy examination revealed no abnormalities. The acute LC50 was determined to be greater than 5.1 mg/L (5,100 mg/m^3).

Discussion

Almost nothing is known about the inhalation effects of GBL. After searching the literature the only inhalation study found was an LC50 study in rats (Monsanto, 1991). This LC50 study did not identify an accurate lethal concentration since none of the animals died during the 4 hour exposure or during the 14 day observation period. The authors noted that hypoactivity was prevalent during the exposure period. The observation of “hypoactivity” seems to indicate that GBL can cause sedation when animals are exposed via the inhalation route. This supports the hypothesis that GBL is absorbed through the lungs. It is reasonable to assume that other systemic effects would be observed if extended inhalation experiments were performed. Given that similar neurological effects were observed in animals dosed via inhalation and oral routes of exposure it was deemed appropriate to use oral toxicity data to evaluate the inhalation health risk of GBL.

There are several oral toxicity studies on GBL. The administration of GBL by gavage to rats and mice at levels up to and including lethal doses did not produce any major histopathologic lesions (NTP, 1992). The most notable effects observed in the 2-year gavage study performed by the National Toxicology Program were that the survival of male mice was significantly lower than that of the controls and that this effect was due to increased aggression as observed by fighting. The incidence and magnitude of aggressive behavior was not measured. There was also a marginal increase in the incidence of pheochromocytomas (benign or malignant combined) in low-dose male mice compared to controls, although neither the trend test nor the pair-wise comparison was statistically significant. The NTP stated that the lack of dose response may be related to the reduced survival in the high-dose group. In female mice there was no apparent increase in the incidence of adrenal medulla proliferative lesions associated with the administration of GBL. Because the trend test was not statistically significant it was deemed inappropriate to use the incidence of pheochromocytomas and adrenal medulla hyperplasia in male mice in the development of a screening level. The decrease in body weight observed in female mice (both 262 and 525 mg/kg; see Table 1) was unaccompanied by organ weight or histopathological changes. In high-dose female rats (450 mg/kg) there was a significant decrease in body weigh compared to controls which was also unaccompanied by organ weight or histopathologic changes. There were no effects observed in either the male rats dosed chronically with 112 mg/kg and 225 mg/kg; however, in the 13-week study, NTP mentioned that the rats dosed with 225 mg/kg were slightly inactive after dosing, indicating a sedative (neurological) effect. A LOAEL of 225 mg/kd was identified based on these sedative effects. A NOAEL of 112 mg/kg in male rats was also identified.

Concerning the neurological effects of GBL, it is known from acute human exposures that GBL causes CNS depression (e.g., sleep, dizziness) and at elevated levels (i.e., “overdose”) GBL can induce coma. GBL is also reported to be psychotropic, producing a “high” (Chin et al, 1992) and in an overdose report GBL produced a “violent aggression” (Li et al, 1998). Increased aggression was also observed in the male mice chronically dosed with 262 and 525 mg/kg/day, and sedative effects were observed in male rats dosed with 225 mg/kg (NTP, 1992). Unfortunately, the subtle behavioral effects of GBL have not been studied in animal models; therefore, no threshold for these effects could be established. However, in a controlled human clinical trial Rosen et al. (1997) observed that volunteers given 30 mg/kg GHB had increased incidences of subjective responses like “sluggish,” “high” and “carefree.”

Thus GHB caused neurological effects in humans at a dose nearly 10 times lower than effects caused by GBH in male rats (30 vs. 225 mg/kg). This points to the possibility that the lowest adverse effect level for GBL is below 225 mg/kg. However, given that the toxicokinetics of GHB and GHL are sufficiently different, a direct comparison should be made with caution. Nonetheless, neurological effects are the most sensitive endpoint for both GBL and GHB.

Derivation of the Screening Level

GBL is rapidly absorbed in the blood after oral dosing. It is reasonable to assume that the systemic effects observed after oral exposure would also occur after inhalation health risk of GBL. Human toxicity data on GBL was found to be inadequate to use to develop a screening level. The best study available on the toxicity of GBL was performed by the National Toxicology Program (NTP, 1992). A NOAEL of 112 mg/kg was identified from this study. It was deemed appropriate to use this effect level to develop an RfD which was subsequently used to develop the screening level. The RfD was developed as follows:

$RfD = (NOAEL \times 5/7)/(UF_1 \times UF_2 \times UF_3)$

Where, the NOAEL (no-observed-adverse-effect-level) is 112 mg/kg (male rat, chronic),
UF_1 is an uncertainty factor of 10 for interspecies extrapolation
UF_2 is 10 for sensitive subpopulations, and
UF_3 is 10 for an incomplete toxicity database.

An uncertainty factor of 10 was chosen for the incomplete database because there were no reproductive studies performed using GBL, but more importantly, the most sensitive endpoint, namely neurobehavioral, was not analyzed quantitatively. The RfD then becomes:

$RfD = [(112\ mg/kg) \times 5/7] \div 1000$

$RfD = 0.08\ mg/kg$

The ITLS was calculated from the RfD based on Rule 232(1)(b) as follows:

$ITSL = RfD \times 70kg/20m^3$

$ITSL = 0.08\ mg/kg \times 70kg/20m^3$

$ITSL = 0.28\ mg/m^3$

$ITSL = 280\ \mu g/m^3$ (based on a 24-hour averaging time)

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