Creatine Monohydrate

bw	body weight
CNS	Chinese Nutrition Society
CRN	Council for Responsible Nutrition
DRI	dietary reference intake
EC SCF	European Commission Scientific Committee on Food
EFSA	European Food Safety Authority
EVM	Expert Group on Vitamins and Minerals
HOI	highest observed intake
ICMR-NIN	Indian Council of Medical Research - National Institute of Nutrition
IOM	Institute of Medicine
IU	international unit
JECFA	Joint FAO/WHO Expert Committee on Food Additives
KNS	Korean Nutrition Society
LOAEL	lowest observed adverse effect level
LOEL	lowest observed effect level
NDA	EFSA Panel on Nutrition, Novel Foods and Food Allergens
NIH	National Institutes of Health
NOAEL	no observed adverse effect level
NOEL	no observed effect level
RCT	randomized clinical trial
SUL	safe upper level
UF	uncertainty factor
UL	tolerable upper intake level

Introduction

Creatine is a naturally occurring amino acid-like compound synthesized in the liver, kidneys, and pancreas from the amino acids arginine, glycine, and methionine (Balsom et al. 1994; Kreider et al. 2022). In the body, creatine occurs as free creatine or phosphocreatine and plays an important role in cellular energy metabolism and related cellular processes (VKM 2016; Kreider et al. 2022; Ostojic 2021). In its phosphorylated intracellular form as creatine phosphate, creatine provides the high energy phosphate for adenosine triphosphate (ATP). Creatine also has a role in translocating energy intermediates from the electron transport system in the mitochondria to the cytosol

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(Kreider et al. 2022).

On average, approximately 2 g of creatine is used per day to maintain normal body cellular energy in humans, with use potentially reaching up to 4 g per day in athletes (VKM 2016; Ostojic 2021). Creatine is synthesized by the body at approximately 1 g per day, consumed in the diet at approximately 1 g per day, and obtained through dietary supplementation (VKM 2016; Balestrino and Adriano 2019; Kreider et al. 2022; Ostojic 2021). Dietary sources include meat, poultry, and fish (Ostojic 2021). Creatine monohydrate is the predominant form used in dietary supplements; other forms include anhydrous creatine, creatine hydrochloride, creatine ethyl ester, buffered creatine, magnesium creatine chelate, and various other creatine salts, such as creatine nitrate, creatine pyruvate, and creatine citrate (Kreider et al. 2022; Jäger et al. 2011; Hezave et al. 2010; Ostojic 2025). Other designations one may see on creatine include references to particle size, such as "micronized" or "instantized"; however, these are only manufacturing specifications and do not meaningfully alter the safety assessment presented here. Recommended dosing for supplement use varies, generally starting with an initial loading phase (e.g., 20 g per day) for 5-7 days followed by a maintenance dose of 3 to 5 g per day (Ostojic 2025).

All supplemental studies including a form of creatine were included in the literature search for this chapter. However, very few studies were identified that met the inclusion criteria for forms other than creatine monohydrate. At least one study each was identified that administered creatine hydrochloride, creatine citrate, creatine pyruvate, or magnesium creatine chelate; however, there were not enough studies to support derivation of an UL or HOI value for these other forms.[1] It is possible that, with additional data, a future assessment may be feasible for these forms, particularly for some creatine salts, given their similar bioavailability to creatine monohydrate (Kreider et al. 2022). Therefore, this chapter focuses on the derivation of an HOI value for supplemental creatine monohydrate (approximately 87.9% creatine) in adults. The HOI is defined as the highest level of intake observed or administered as reported within studies of acceptable quality. Creatine referred to herein reflects creatine monohydrate, unless otherwise specified.

[1] All studies with creatine doses informing the CRN HOI (i.e., >5 g per day for a duration >7 days) were conducted with creatine monohydrate, except for 3 studies that did not specify form. However, these are assumed to also be creatine monohydrate based on year of publication (Murphy et al. 2005; Hersch et al. 2006; Gualano et al. 2008a).

Bioavailability

The degradation of creatine to creatinine during digestion is less than 1%, as the low pH of the stomach prevents intramolecular cyclization (Kreider et al. 2022). Orally ingested creatine is absorbed from the gastrointestinal tract via active transport and then transported through the bloodstream to tissues (Orsenigo et al. 2005; Speer et al. 2004; Peral et al. 2002; VKM 2016). Approximately 95% of the body's total creatine is stored in skeletal muscle (VKM 2016). The remaining 5% of the creatine pool is distributed between the brain, liver, kidney, and testes (Ostojic 2021; Kreider et al. 2017, 2022). The bioavailability of creatine is nearly complete, with ~99% of the ingested creatine absorbed into tissues and the remainder excreted undegraded in the urine (Kreider et al. 2022).

Muscle creatine concentrations reach around 60-80% saturation from a typical dietary intake of 1-2 g of creatine per day (Kreider et al. 2017). Excess creatine in skeletal muscle non-enzymatically degrades into creatinine and is excreted through the kidneys in urine (VKM 2016; Kreider et al. 2022; Ostojic 2021). In healthy individuals, creatinine is neither reabsorbed nor affected by urine flow. Retained creatinine in the blood may be a key sign of renal impairment (VKM 2016).

Safety Considerations

No serious adverse events have been associated with supplemental creatine in human clinical trials. As reviewed herein (see *Human Clinical Studies*), creatine has been the subject of hundreds of clinical trials in various populations, with no serious adverse events and only limited side effects (i.e., *nuisance effects*; see CRN's Methodology) reported. Recent review articles and systematic reviews have also reached the same conclusions for healthy adults and individuals with various disease states (Balestrino and Adriano 2019; Ostojic 2021; Naeini et al. 2025; Longobardi et al. 2025; ISSN 2025; Kreider et al. 2025). The International Society of Sports Nutrition (2025; Kreider et al. 2017) issued the following statement, "the robust body of evidence supports the safety and multifaceted benefits of creatine supplementation across all age groups," based on multiple considerations, including the results of a recent systematic review published by Kreider et al. (2025).

Kreider et al. (2025) compared adverse event reporting across 685 creatine trials and their available placebo groups. The analysis encompassed 12,839 creatine recipients from 685 studies and 13,452 placebo recipients from 652 studies; mean creatine exposure was approximately 12.5 g per day when body-weight-based regimens were standardized. The proportion of studies reporting any side effect was similar for creatine and placebo (13.7% and 13.2%, respectively). Across all 49 evaluated adverse events, the overall pattern and total participant-level frequency were not significantly different between creatine and placebo groups (4.60% vs. 4.21%).

As noted by the previous CRN safety assessment, media reports of links between creatine use and muscle strains, muscle cramps, heat intolerance, and other side effects are not supported by the scientific literature (Shao and Hathcock 2006). As demonstrated below in *Human Clinical Studies*, extensive studies conducted in athletes, healthy adults, and diseased populations substantiate the safety of creatine use in most healthy adults.

Kidney Function

Historically, the principal safety question concerning supplemental creatine has involved possible effects on kidney function. Early concern that high creatine intake might damage the kidneys arose largely from isolated human case reports, including a report involving preexisting renal disease, and from findings in an animal model of renal impairment (Shao and Hathcock 2006; Longobardi et al. 2025). Because creatine and its breakdown product, creatinine, are cleared by the kidneys, supplementation can increase circulating or urinary concentrations of these compounds without necessarily indicating renal injury. Serum creatinine, urea, albuminuria, and measures of filtration or clearance are commonly considered together when renal function is evaluated. Across controlled and uncontrolled supplementation trials, increases in serum or urinary creatine and creatinine have generally remained within expected clinical ranges and have not been accompanied by consistent evidence of impaired filtration or other kidney damage. Once skeletal-muscle creatine stores are saturated, they may remain elevated for several weeks after supplementation stops (Snow and Murphy 2003). Continued intake beyond that needed to maintain tissue stores can increase the amount converted to creatinine and eliminated in urine (Pline and Smith 2005). Thus, a modest rise in serum creatinine or a creatinine-based reduction in

estimated glomerular filtration rate may reflect altered creatine metabolism rather than a true decline in kidney function. Renal status should therefore be interpreted from the overall clinical picture and, when appropriate, from markers that are less dependent on creatinine metabolism. Reviews of the clinical literature and expert evaluations have consistently found no evidence that creatine supplementation impairs kidney function in healthy individuals (e.g., Poortmans and Francaux 2000; Yoshizumi and Tsourounis 2004; Pline and Smith 2005; Longobardi et al. 2025; Kreider et al. 2017, 2025). Naeini et al. (2025) systematically reviewed 21 studies and found a small increase in serum creatinine with creatine use but no significant difference in glomerular filtration rate compared with control groups. The authors interpreted the creatinine change as a consequence of creatine turnover rather than renal dysfunction. Taken together, the available evidence supports preserved kidney function in healthy adults using supplemental creatine, while also showing that creatinine-based laboratory values should be interpreted with awareness of creatine intake. These findings are supported by a systematic review by Kreider et al. (2025), which found that renal-function markers did not differ significantly between creatine and placebo participants. In addition, among the studies reviewed in CRN's assessment that evaluated kidney function, no significant adverse changes in renal markers were identified (e.g., Kreider et al. 1998, 2003; Gualano et al. 2008a,b; Groeneveld et al. 2005; Chilibeck et al. 2023).

Accordingly, supplemental creatine is not associated with clinically meaningful impairment of kidney function in healthy adults at the intakes evaluated in human studies. However, evidence is more limited in individuals with existing renal disease or dysfunction, and changes in serum creatinine can complicate clinical interpretation. Until additional data are available, individuals with impaired kidney function are excluded from the target population for CRN's HOI. Individuals should consult a healthcare provider before using creatine supplements.

Gastrointestinal Effects

The side effect most often associated with creatine in clinical research is gastrointestinal discomfort, particularly when a large single dose is not fully absorbed. However, this finding has not been consistently observed across studies (Kreider et al. 2017; Ostojic 2025; Longobardi et al. 2025). Kreider et al. (2025) reported that gastrointestinal complaints were noted in 4.9% of creatine groups and 4.3% of placebo groups. When the analysis was based on affected

participants, gastrointestinal complaints occurred in 5.51% of creatine recipients and 4.05% of placebo recipients, and the difference was not statistically significant. Gastrointestinal discomfort is considered a *nuisance effect* and not a *true hazard* (as defined in CRN's Methodology); however, the frequency of gastrointestinal side effects reported in clinical trials with creatine (primarily diarrhea) suggests that dividing the total daily intake into servings no larger than 5 g provides a conservative measure to reduce potential gastrointestinal discomfort. This provision is based conservatively on data regarding gastrointestinal symptoms relative to creatine dose from select studies (e.g., Ostojic and Ahmetovic 2008).

Muscle Cramps

Issues with thermoregulation and muscle cramps have also been reported with supplemental creatine; however, this finding has not been consistent across studies (Kreider et al. 2017; Longobardi et al. 2025). Kreider et al. (2025) reported that muscle cramping or pain was reported in 2.9% of creatine recipients and 0.9% of placebo recipients, respectively. When the analysis was based on the number of affected participants rather than the number of studies, muscle cramping or pain occurred in 0.52% and 0.07%, respectively, and was not statistically significant. In addition, muscle cramping is considered a *nuisance effect* and not a *true hazard* (as defined in CRN's Methodology) and is not considered in the derivation of an HOI.

Cancer

Evidence regarding creatine and cancer is mixed and remains largely mechanistic or preclinical data. Some studies suggest that creatine may reduce cancer risk in certain populations or support recovery after treatment (Kreider et al. 2025; Jiang et al. 2025). Other laboratory and animal studies have raised concern that creatine could supply energy as ATP to cancer cells and thereby support tumor progression (ONS 2026; Zhang and Bu 2022). When considered together, the experimental evidence is mixed, as creatine-related energy metabolism has been associated with both tumor progression and antitumor activity, depending on the model and biological context. These divergent findings cannot currently be translated into definitive conclusions about supplemental creatine use in humans. Additional clinical evidence is therefore needed before firm conclusions or population-specific recommendations can be made. As a precaution, individuals

with active cancer should consult their healthcare provider before using creatine supplements; however, the available evidence does not currently warrant exclusion of this population from CRN's HOI.

Human Clinical Studies

The previous CRN safety assessment derived a supplemental HOI (5 g per day) based on data from double-blind, randomized, controlled human trials (Shao and Hathcock 2006). A large volume of human intervention studies published since that time were identified with potential relevance to this update.[2] Two hundred seven human clinical trials published since 2005 were identified that met the inclusion criteria (see CRN Methodology Chapter). Of the 207 studies, 45 were determined to have administered a high loading dose only, generally 20-21 g per day for 7-8 days, and were not further assessed. Of the remaining 162 studies, 102 administered non-loading doses of 5 g per day or less for at least 7 days. Because no serious adverse events are known for supplemental creatine, this review focused on studies using doses above 5 g per day that could inform the HOI. Fifty-two studies, represented in 60 publications, from the updated search and six studies from the previous CRN safety assessment are summarized below (58 studies in total). No serious adverse events attributable to creatine supplementation were reported, although not all studies were specifically designed to assess such effects.

Ten studies administered 20 to ~30 g creatine per day for durations ranging from 1 week to 4 years (Hersch et al. 2017; Atassi et al. 2010; Rosas et al. 2014; Babu et al. 2020; Huerta Ojeda et al. 2024; Poortmans et al. 2005; Connell et al. 2021; del Favero et al. 2012; Moriarty et al. 2023; Smith et al. 2025). Hersch et al. (2017) conducted a multicenter, double-blind, randomized, placebo-controlled trial in patients with early symptoms of Huntington's disease. Patients (n=553) received placebo or creatine for up to 48 months; the dose of creatine varied based on tolerability from 5-40 g per day (mean of 31.6 g per day). The number of patients per actual dose was not provided. The authors concluded that "no safety concerns were noted." The authors also reported "[m]ild, unexplained, asymptomatic elevations of creatine phosphokinase were more frequent in creatine-treated participants," and noted these effects have only been observed in this one study

[2] Literature search conducted June 2026

with Huntington's disease patients. The relevance of this finding is unclear, especially to the general population (Hersch et al. 2017). This same group published a smaller, long-term study, which administered placebo or creatine up to 30 g per day to patients (n=64) diagnosed with asymptomatic Huntington's disease or individuals at risk of developing the disease for 18 months (Rosas et al. 2014). More than two-thirds of the treated group reached 30 g creatine per day in this study, but specific data regarding doses were not provided. Babu et al. (2020) conducted a dose selection study in amyotrophic lateral sclerosis (ALS) patients who received tamoxifen (n=40) or 30 g creatine per day (n=20) for 266 days. While most events were not serious (e.g., gastrointestinal effects), deep vein thrombosis was mentioned. While it is unlikely that this event was attributable to creatine based on its known effects in the body, the frequency of side effects reported in this publication were unclear and statistical significance could not be assessed based on the data as presented. One short dose escalation study was identified that administered 10, 20, and 30 g creatine per day each for a week progressively (Atassi et al. 2010). No adverse events were reported in this study. Four RCTs and two single-arm trials tested creatine at doses between 20-21 g per day. The longer duration studies included a RCT published by Moriarty et al. (2023), in which 30 healthy, young adults received 0, 10, or 20 g creatine per day for 6 weeks (n=10 per dose) and a single-arm trial by Smith et al. (2025), in which Alzheimer's disease patients (n=20) received 20 g creatine per day for 8 weeks. The remaining studies in this dose range were short-term, ranging from 9-14 days (Huerta Ojeda et al. 2024; Poortmans et al. 2005; Connell et al. 2021; del Favero et al. 2012).

Five intervention studies tested creatine at doses ranging from 11.2 to 16 g per day (Godlewska et al. 2024; Kreider et al. 1998; Mert et al. 2017; Tang et al. 2014; Eijnde et al. 2005). One small, uncontrolled feasibility study included 14 patients with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) that were given 16 g creatine per day for 6 weeks (Godlewska et al. 2024). The remaining four studies with creatine doses between 11.2 and 15.75 g per day were conducted in male athletes or bodybuilders (Kreider et al. 1998; Mert et al. 2017; Tang et al. 2014) or healthy young adults (Eijnde et al. 2005). Kreider et al. (1998) conducted a double-blind, randomized, placebo-controlled trial in American college football players. Participants received 0 (n=14) or 15.75 (n=11) g per day for 28 days. The mean body weight of participants was 97.2 kg, much greater than the default values of 60 kg or 70 kg typically used in risk assessment. The authors stated that the supplement was well tolerated but noted that the results provided "some evidence of

a mild elevation in creatine kinase (CK), lactate dehydrogenase (LDH), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) activities in the HP [creatine] group with no effects on g-glutamyltransferase (GGT).” Of note, no significant changes in biochemical markers related to liver were identified in other studies including such (e.g., Chilibeck et al. 2023; Atassi et al. 2010; Bennet et al. 2001). Further studies include a ≥4-week observational study in bodybuilders taking 3.5-15 g creatine per day (mean of 7.5 g per day) (Mert et al. 2017); a double-blind trial in healthy, young volunteers (n=22) receiving 0 or 15 g per day for 2 weeks (Eijnde et al. 2005); and an experimental intervention study in male athletes administered 12 g per day for two nonconsecutive 15-day periods (Tang et al. 2014).

Fifteen double-blind, randomized trials evaluated creatine at approximately 10 g per day across diverse populations and durations (Kieburtz et al. 2015; Groeneveld et al. 2005; NINDS NET-PD Writing Group 2006; Chilibeck et al. 2023; Kendall et al. 2009; Ostojic and Ahmetovic 2008; Walter et al. 2000; Kornblum et al. 2005; Hoffman et al. 2006; Arciero et al. 2001; Watsford et al. 2003; Gualano et al. 2008a,b; Murphy et al. 2005; Sanchez-Gonzalez et al. 2011; Stout et al. 2007). The largest and longest was a multicenter, parallel-group trial by Kieburtz et al. (2015), in which 1,741 patients with Parkinson’s disease (874 assigned to creatine) received 0 or 10 g creatine per day for 5–8 years. There were no detectable differences in the incidence of side effects between groups. Two additional RCTs administered the same doses (0 or 10 g creatine per day) in patients with neurological disorders. Groeneveld et al. (2005) followed 175 patients with ALS (88 receiving creatine) for 310 days, reporting no statistical differences in side effects between groups. The NET-PD Writing Group (2006) included 200 asymptomatic patients (n=67 in the creatine group) with Parkinson’s disease for 12 months; no serious adverse events were attributed to creatine in this study. Chilibeck et al. (2023) similarly compared 0 and 10 g creatine (n=120) per day for 2 years in 237 postmenopausal women, with no significantly increased side effects attributed to creatine supplementation. Shorter trials included Kendall et al. (2009), involving 42 active males (21 receiving creatine), and Ostojic and Ahmetovic (2008), involving 59 top-level male soccer players (40 receiving creatine), each conducted for 30 days. Walter et al. (2000) used a crossover design in 36 dystrophic patients to evaluate 0 and 5–10 g creatine per day over 2 months, although the number of participants receiving each dose was unclear. The remaining studies provide additional support for the safe use of creatine at approximately 10 g per day but each had limitations attributed to short duration and/or small study size, as reported by

Kornblum et al. (2005), Hoffman et al. (2006), Arciero et al. (2001), Watsford et al. (2003), Gualano et al. (2008a,b),[3] Murphy et al. (2005), Sanchez-Gonzalez et al. (2011), and Stout et al. (2007). Collectively, the available studies at 10 g creatine per day extend the evidence base to clinical, athletic, and generally healthy populations.[4]

Twenty-eight additional intervention studies administered creatine at doses ranging from 6-8 g per day at durations ranging from 10 days to 1 year (Hersch et al. 2006; Slankamenac et al. 2024; Chilibeck et al. 2007; Forbes et al. 2017; Kresta et al. 2014; Li et al. 2025; Little et al. 2008; Pakulak et al. 2022; Olsen et al. 2006; Bender et al. 2005; Roschel et al. 2021; Chrusch et al. 2001; Bennett et al. 2001; Rosene et al. 2009; Amiri and Sheikholeslami-Vatani 2023; Bonilla et al. 2021; Brooks et al. 2023; Butchart et al. 2022; Candow et al. 2008, 2014, 2021; Cooke et al. 2009; Cornish et al. 2009; Cribb et al. 2007; Fuld et al. 2005; Ormsbee et al. 2012; Toniolo et al. 2017, 2018). No serious adverse events were reported. In studies that presented comparative data, side effect rates were not significantly different between groups.

Of note, a large portion of the clinical trials conducted with creatine using healthy adults have used a "loading phase" (typically 20 g creatine per day) for 3 days to 1 week in duration, followed by a "maintenance phase" at a lower dose and of varying duration. The rationale is that the large dose for a short period at the outset of supplementation may help facilitate creatine uptake by skeletal muscle (Bemben and Lamont, 2005). For the purposes of this review, rather than being used as the basis for short-term recommendations, which are outside the scope of an HOI or UL, loading doses were only considered as support for recommendations for a lower maintenance dose deemed safe for long-term use. Of those studies reviewed by CRN as part of this assessment, the vast majority of studies also using a loading dose were those with a maintenance dose of 8 g creatine per day or less; only five studies at 10 g creatine per day during the maintenance phase also included a higher loading dose (Arciero et al. 2001; Watsford et al. 2003; Gualano et al. 2008a,b; Murphy et al. 2005; Stout et al. 2007).[5]

[3] Gualano et al. (2008a,b) published two manuscripts on the same study.
[4] Five of these studies also included a loading dose (Arciero et al. 2001; Watsford et al. 2003; Gualano et al. 2008a,b; Murphy et al. 2005; Stout et al. 2007).
[5] These studies corroborated but were not used for derivation of the HOI.

Official Reviews

IOM. The IOM has not derived an UL value for creatine.

EC SCF (2000) and EFSA (2004). In 2000, the EC SCF reviewed the available data on creatine supplementation from "many efficacy trials," noting that large-scale, well-controlled studies were lacking at that time. The Committee determined that lower doses of up to 3 g per day were "unlikely to pose any risk." Regarding high loading doses (described as 10 to 50 g per day for 5 to 7 days), the EC SCF stated that long-term data were insufficient to support a safety conclusion, despite a lack of adverse events in available studies. These conclusions were carried forward and extended to creatine monohydrate by the EFSA (2004). Neither the EC SCF nor the EFSA have assessed creatine for the purposes of deriving an UL value.

EVM (2003). The UK's EVM has not derived an UL value for creatine.

CNS (2023). The CNS has not derived an UL value for creatine.

ICMR-NIN (2020). The ICMR-NIN has not derived an UL value for creatine.

KNS (2020). The KNS has not derived an UL value for creatine.

CRN Recommendations

CRN previously derived a supplemental HOI[6] value for creatine monohydrate of 5 g per day in adults (Shao and Hathcock 2006). The goal of the current chapter was to determine whether more recent human clinical data are available that might impact the previous conclusions. While not all human clinical trials are specifically designed to evaluate adverse events, no new trials were identified that reported any serious adverse events with supplemental creatine. Following CRN's methodology (see Methodology Chapter), and due to the lack of any known adverse

[6] The term "Observed Safe Level" or OSL used by Shao and Hathcock (2006) is interchangeable with HOI.

effects for creatine, an HOI is derived by CRN in this update. As with any assessment in which not all available data are reviewed, inherent uncertainties with the risk assessment and selection of the HOI are recognized.

CRN's safety methodology for deriving supplemental HOI values prioritizes data from human clinical studies when available. The tables below summarize the key human clinical studies considered in deriving the supplemental HOI value by CRN according to its principal points of departure for risk assessment (as described in the Methodology Chapter).[7] Table 1 summarizes higher dose clinical studies that were considered for developing the HOI but ultimately were given less weight due to limitations described in the table. The key studies presented in Table 2 provide the most reliable and consistent evidence under CRN's Methodology, as they include controlled designs, varied adult populations, and exposure periods ranging from 1 month to as long as 5–8 years. As discussed in *Safety Considerations*, no serious adverse events were reported in any of the studies reviewed.

[7] Where numerous relevant studies were identified, those most pertinent to the HOI derivation are included in the table as representative studies. Prioritization was given to studies at dose levels informing the HOI and studies with higher weighting based on CRN's methodology (e.g., duration, number of participants, randomization, etc.).

Table 1. Higher-Dose Studies Considered for the CRN HOI for Creatine Monohydrate in Adults

Reference	Study Design	Participant Description	No. of Subjects Total	No. of Subjects at Highest Dose	Supplemental Dose(s) (g/day)	Duration[a]	Study Limitations for HOI Considerations
Studies from Shao and Hathcock (2006)							
Kreider et al. 1998	Double-blind, randomized, placebo-controlled	American college football players	25	11	0, 15.75	1 month	Small size; shorter duration
Studies identified in update							
Hersch et al. 2017	Multicenter, double-blind, randomized, placebo-controlled	Patients with early symptoms of HD	553	Unclear (275 total in creatine group)	0, 5-40 (mean 31.6)	≤48 months	Dosing varied due to tolerability; number of patients per finished dose not provided
Rosas et al. 2014	Double-blind, randomized, placebo-controlled	Asymptomatic participants with premanifest (tested) and at-risk (not tested) for HD	64	Unclear (32 with >21 tolerating 30 g/day)	0, ≤30	18 months	Small size with 2/3 of creatine group reaching 30 g/day
Babu et al. 2020	Double-blind, randomized, double-dummy	Patients with ALS	60	20	0, 30	~9 months	Small size; no placebo control; frequency and statistical significance of one serious AE could not be evaluated[b,c]
Smith et al. 2025	Single-arm pilot	Patients with AD	20	20	20	2 months	Small size; no control group
Moriarty et al. 2023	Double-blind, randomized, placebo-controlled	Healthy young adults	30	10	0, 10, 20	1.5 months	Small size; shorter duration

Reference	Study Design	Participant Description	No. of Subjects Total	No. of Subjects at Highest Dose	Supplemental Dose(s) (g/day)	Duration[a]	Study Limitations for HOI Considerations
Godlewska et al. 2024	Uncontrolled feasibility	Patients with ME/CFS	14	14	16	1.5 months	Small size; shorter duration; no control group

Abbreviations: AD, Alzheimer's disease; AE, adverse event; ALS, amyotrophic lateral sclerosis; HD, Huntington's disease; ME/CFS, Myalgic encephalomyelitis/chronic fatigue syndrome

[a] Where relevant, durations were converted to months based on 4 weeks per month and 12 months per year.

[b] The other two groups denoted as "0" g per day received tamoxifen (i.e., there was no placebo control group).

[c] Deep vein thrombosis (DVT)

Table 2. Studies Considered to Derive the CRN HOI for Creatine Monohydrate in Adults

Reference	Study Design	Participant Description	No. of Subjects Total	No. of Subjects in Highest Dose Group	Supplemental Dose(s) (g/day)	Duration[a]
Key studies from Shao and Hathcock (2006)						
Groeneveld et al. 2005	Double-blind, randomized, placebo-controlled	Patients with ALS	175	88	0, 10	10 months
Walter et al. 2000	Double-blind, randomized, crossover	Dystrophic patients	36	Unclear	0, 5-10	2 months
Key studies identified in update						
Kieburtz et al. 2015	Multicenter, double-blind, parallel-group, randomized, placebo-controlled	Patients with Parkinson's disease	1,741	874	0, 10	5-8 years
Chilibeck et al. 2023	Double-blind, randomized, placebo-controlled	Postmenopausal women	237	120	0, 10	2 years
NINDS NET-PD Writing Group 2006	Phase II, double-blind, randomized, placebo-controlled	Asymptomatic patients with Parkinson's disease	200	67	0, 10	1 year
Kendall et al. 2009	Double-blind, randomized, placebo-controlled	Active males	42	21	0, 10	1 month
Ostojic and Ahmetovic 2008	Double-blind, randomized, placebo-controlled	Top-level male soccer players	59	40	0, 10	1 month

Abbreviations: ALS, amyotrophic lateral sclerosis; HD, Huntington's disease

[a] Where relevant, durations were converted to months based on 4 weeks per month and 12 months per year.

Creatine has not been evaluated by authoritative agencies, such as the IOM, the EFSA, or the EVM (2000), for the purposes of deriving an UL (see *Official Reviews*). Creatine has been

extensively reviewed and consistently concluded to be safe for most populations based on a lack of serious adverse events in available studies (Kreider et al. 2025; ISSN 2025). As discussed herein, no serious adverse events or *true hazards* (as defined in CRN's Methodology Chapter) have been reported in human intervention trials with supplemental creatine.

As discussed in the *Safety Considerations* section, gastrointestinal symptoms and elevations in serum creatinine were reported more frequently in higher dose studies (e.g., >10 g per day). Based on the available dataset, these findings were transient or clinically non-adverse and did not constitute *true hazards* under CRN's Methodology. Nonetheless, the frequency of gastrointestinal side effects reported in clinical trials with creatine (primarily diarrhea) suggests that dividing the total daily intake into servings no larger than 5 g provides a conservative measure intended to reduce potential gastrointestinal discomfort.

Across the 162 publications reviewed as part of this update, no serious adverse events attributed to supplemental creatine were reported. Of these, fifteen studies administered >10 and up to ~30 g creatine per day for durations ranging from 1 week to 4 years (Hersch et al. 2017; Atassi et al. 2010; Rosas et al. 2014; Babu et al. 2020; Huerta Ojeda et al. 2024; Poortmans et al. 2005; Connell et al. 2021; del Favero et al. 2012; Moriarty et al. 2023; Smith et al. 2025; Godlewska et al. 2024; Kreider et al. 1998; Mert et al. 2017; Tang et al. 2014; Eijinde et al. 2005). Although no serious adverse events were attributed to creatine in these higher-dose studies (i.e., >10 g per day), each study has important limitations for establishing an HOI. As summarized in Table 1, these include small sample sizes, short exposure periods, uncontrolled or single-arm designs, dose adjustments prompted by tolerability, and/or incomplete reporting of the number of participants maintained at the highest dose. Consequently, these studies are used as supportive evidence rather than as the primary basis for selecting the HOI.

Clinical studies in patients, particularly those with neurological disorders were retained in CRN's assessment because the available evidence does not indicate a disease-specific alteration in creatine utilization or systemic exposure that would make the safety findings in these populations irrelevant. Nevertheless, the largest and longest higher-dose studies were conducted primarily in participants with neurological disorders, including Huntington's disease, ALS, and Alzheimer's disease. Differences in health status, treatment context, and clinical monitoring limit direct

extrapolation to the general adult population. As such, these data are considered together with controlled studies in healthy or more broadly representative adults. Similarly, the higher dose study in collegiate football players is not considered directly relevant to the general population because the participants' mean body weight of 97.2 kg yielded a substantially lower dose on a body-weight basis than would result from applying the same absolute dose to the 60- or 70-kg default adult body weights used in standard risk assessment. In addition, as described in the *Introduction*, creatine turnover may be higher in athletes than in nonathletes, further limiting direct extrapolation from this single athletic cohort.

For derivation of the CRN HOI, the most robust dataset consists of human intervention studies administering 10 g creatine per day (Kieburtz et al. 2015; Groeneveld et al. 2005; NINDS NET-PD Writing Group 2006; Chilibeck et al. 2023; Kendall et al. 2009; Ostojic et al. 2008; Walter et al. 2000; Kornblum et al. 2005; Hoffman et al. 2006; Arciero et al. 2001; Watsford et al. 2003; Gualano et al. 2008a,b; Murphy et al. 2005; Sanchez-Gonzalez et al. 2011; Stout et al. 2007). The key studies presented in Table 2 provide the most reliable and consistent evidence under CRN's Methodology as they include controlled designs, varied adult populations, and exposure periods ranging from 1 month to as long as 5–8 years. Across these studies, 10 g per day was not associated with serious adverse events.

Based on the human studies available, 10 g creatine per day is selected as the supplemental NOAEL[8] for adults following the CRN process. As described in CRN's Methodology, if the supplemental intake dose-response relationship is identified from the strongest data and assessed conservatively, no additional uncertainty factor is needed (that is, the implicit UF is 1.0). Consistent with CRN's methodology, an UF of 1 is applied to yield an HOI of 10 g per day for adults for supplemental creatine monohydrate. CRN recommends that creatine doses be divided into doses no larger than 5 g each to minimize potential gastrointestinal discomfort.

The HOI is defined as the highest level of intake observed or administered as reported within studies of acceptable quality. Although limitations of the higher-dose studies prevent them from independently establishing the HOI, their consistency and, in some cases, duration, increase

[8] The term "NOAEL" is used here for consistency with CRN's Methodology. However, this use refers to a "hanging NOAEL," meaning no adverse effects observed.

confidence that the absence of adverse events likely extends above 10 g per day in healthy adults.

Until additional data become available to assess safety in individuals with impaired kidney function, this population is excluded from the target population for the HOI and should consult with a healthcare provider before supplementing with creatine. In addition, as a precaution, individuals with active cancer should consult their healthcare provider before using creatine supplements; however, the available evidence does not currently warrant excluding this population from CRN's HOI.

Unlike vitamins and minerals, creatine is not a standard nutrient and is, therefore, typically not evaluated for the purposes of setting upper intake levels or limits. Nevertheless, relevant information from each of the organizations summarized in the *Official Reviews* section is listed below in Table 3.

Table 3. Quantitative Summary for Creatine Monohydrate in Adults

CRN (2026) HOI, supplemental intake	10 g/day (no more than 5 g at one time)[a,b]
IOM UL, total intake	Not evaluated
EC SCF (2000)/EFSA (2004)	Not evaluated for UL; 3 g/day "unlikely to pose any risk"
EVM (2003)	Not evaluated
CNS (2023), total intake	Not evaluated
ICMR-NIN (2020), total intake	Not evaluated
KNS (2020), total intake	Not evaluated

[a] Excludes those with known risk factors related to kidney impairment; such individuals should consult with their healthcare provider. Those with active cancers are also recommended to consult with their healthcare provider.
[b] Recommended dosing to minimize potential gastrointestinal discomfort.

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Updated October 2026 by

ToxStrategies, LLC, a BlueRidge Life Sciences Company